

UNOFFICIAL TRANSCRIPT*
WASHINGTON STATE PHARMACY AND THERAPEUTICS COMMITTEE MEETING
June 15, 2005
Radisson Hotel SeaTac
9:00am – 2:30pm

Committee Attendance:

Daniel Lessler, M.D. (Chair)
Janet Kelly, Pharm.D
Jason Iltz, Pharm.D (Via teleconference)
T. Vyn Reese, M.D.
Angelo Ballasiotes, Pharm.D.
Patti Varley, ARNP
Carol Cordy, M.D. (Vice Chair)
John White, M.D.

A quorum was shown for all Pharmacy & Therapeutics Committee motions, 2nd's, and votes.

9:00 a.m. - Committee came to order.

WELCOME & INTRODUCTIONS

Daniel Lessler, M.D.: [Inaudible] ...pharmacy and therapeutics committee meeting. We have a rather packed agenda so I think in particular I would appreciate when people are giving stakeholder comment, that they could limit their comments to three minutes. I also would just remind anybody that if you have written materials of any sort to submit we ask that you submit those through OHSU, the evidence based practice center. I think Jeff Graham has some additional comments before we get started.

Jeff Graham, M.D.: I just want to bring to your attention that we are having a slight schedule change from drug class reviews. As many of you know we do post our schedule for drug class reviews on our web site. The report for attention deficit disorder drugs used in that disease has been delayed and so our review has been delayed until December for that drug class.

On the A typical anti-psychotic review there is one out as we know, but that will be updated and will be released in January 2006. For that reason we have delayed our review for that drug class until February 2006. There could be a few other slight changes in that schedule and we will be updating the schedule on our web site probably within the next two weeks so feel free to look at that.

I did want to make one other comment. We will be giving information as to which pharmaceutical manufacturers have submitted dossiers on their drug class as we do the new drug classes and in the first class, which is the drugs that treat Alzheimer's. Jansen and Forrest did submit dossiers and comments were made on the draft reports by [Inaudible] and Forrest and we

* For copies of the official audio taped record of this meeting,
please contact Regina Chacon at (206)521-2027 pdp@hca.wa.gov.

appreciate all those pharmaceutical manufacturers for putting in their dossiers and reviewing the draft reports and giving comments on them.

Jeff Graham, M.D.: So on the phone...Jason are you there?

Jason Iltz, Pharm. D.: I am.

Daniel Lessler, M.D.: Great, and Jeff do we have anybody else on the phone?

Jeff Graham, M.D.: Rick Hansen from North Carolina is on the phone.

Daniel Lessler, M.D.: Rick, are you here?

Rick Hansen: I'm here.

Daniel Lessler, M.D.: Okay, thank you. I think we can do...we've got the PowerPoint presentation ready to go. So Rick we're looking at the first slide, just the title slide, Drug Class Review on Alzheimer's disease drugs and now we are on the first slide. If you want to pick it up there and let us know when you want Next slide we'll let you take it from here. Thanks.

Rick Hansen: If I'm correct, these are in order. Okay, I will just say next slide then. Well, good morning everyone. Again, my name is Richard Hansen and I'll be presenting the draft report. Actually, the final report of our systematic review of Alzheimer's drugs and this review was conducted by the Research Triangle Institute and UNC Evidence Based Center here in Chapel Hill, NC.

The review included five different medications used to treat Alzheimer's disease. Four cholinesterase inhibitors and one [Inaudible]. The cholinesterase inhibitors included Donepezil, Galantamine, Rivastigmine, and Tacrine. Memantine is the [Inaudible] and receptor [Inaudible]. Although it was not approved for use in the U.S. until 2003 it has been used in Germany for the treatment of dementia since 1989 and [Inaudible] find European studies that dated back prior to [Inaudible].

The drugs reviewed [Inaudible] vary in their specific mechanism of action and I'll just point you to table one in the forward [Inaudible], which provides a complete summary of drug specific properties including the titration interval and dosing frequencies, which I may reference as we go on today.

Next slides...patient populations living with these diseases in the community, residing in nursing homes were eligible for inclusion in the review. We included all levels of disease severity in mild, moderate [Inaudible] disease.

Next slide...for efficacy and effectiveness we focused on how [Inaudible] measure such as day-to-day function. This included activities of daily activity, mental activities [Inaudible] and changes in the level of care, as well as hospitalization and mortality. Intermediate [Inaudible] for cognition, real symptoms and discontinuation effects of [Inaudible].

Next slide...although practically every disease today relies on a battery of measurement, Alzheimer's disease research utilizes [Inaudible] large variety of health measurements. Common fields can be characterized by their assessment of cognition, global change, function, and [Inaudible].

Jeff Graham, M.D.: Rick, it might help...Rick, are you there? Rick? Are you on a speakerphone?

Rick Hansen: I'm on a cell phone. Is it not coming through well?

Jeff Graham, M.D.: It's much better now.

Daniel Lessler, M.D.: You might have to pull the receiver away a little bit. We are getting a lot of static about every fifth word.

Rick Hansen: Okay, I will try it. Is that better? There was so much feedback with my voice on the other end I was holding it away. Is that better?

Daniel Lessler, M.D.: Yeah, that's better. Give it a try here.

Rick Hansen: Okay, so going back to the common measurement scales. The measurement scales effect cognition, global change, function, and behavior and because of a variety of measures, we included a draft...in the report we included a short summary of the commonly used scales. [Inaudible] usually was assessed in the MMSE(?), A-cog or the [Inaudible] battery. Global change frequently was measured by the CGIC, Civic Plus, the GDS. Measures of functional status commonly included GDS, ABL, the DAD or the [Inaudible] ABL. And behavioral measures included the NPI or behave AD(?).

Next slide...for tolerability and [Inaudible] we assessed the overall adverse effect report, serious adverse event report and adverse events related to discontinuation of treatment. Also we looked at overall loss of follow up and withdrawals because of adverse events. We report on specific adverse events including hepatotoxicity, gastro intestinal symptoms and subsequent weight loss and cardio vascular events.

Next slide...as with previous drug class reviews conducted by the RTI and UNC Evidenced Based Practice Center we differentiated between efficacy trials and effectiveness trials. Studies conducted in primary care or office space settings [Inaudible] including criteria, followed patients for at least one year and primarily assessed how [Inaudible] outcomes rather than intermediate outcomes considered effectiveness trials. All others were considered efficacy trials. For effectiveness and efficacy we included head-to-head comparative trials, meta analyses, and placebo controlled trials. We focused primarily on head-to-head evidence, summarized the general evidence provided by well done systematic reviews and placebo controlled trials. For safety and adverse events we included studies eligible for our effectiveness and efficacy assessment as well as occupational studies. All evidence was included for [Inaudible] or time to assess clinical response as well as per sub group.

Next slide...prior to presenting the findings of our review, I wanted to point out a couple of special considerations we discussed [Inaudible] priority. First we acknowledged the fact that Alzheimer's disease is progressive in nature and very short trials would not be adequate to assess the effect of drug treatment. Therefore, we included trials that were 12 weeks or longer. We also realized that [Inaudible] and the rate of titration to the desired dose varied between drugs and trials. Several of the trials discussed in our review utilized higher doses or faster titration schedules than currently recommended in clinical practice. Although we did not exclude [Inaudible] trials, we point out differences in FDA approved doses or recommended titration schedules especially when there may be implications for efficacy or adverse events.

Next slide...overall comparative evidence for these drugs is limited. We did not identify any comparative trial that we considered to be an effectiveness trial. In fact, we did not identify any randomized double blind, head-to-head trials. We did include three open label head-to-head trials. In these trials authors justified using an open label design because of differences in dosing frequency and titration schedules although this justification is debatable. We included 20 placebo-controlled trials, 7 systematic reviews or meta analyses.

Next slide...two trials compared Donepezil to Galantamine. One was a 52-week open label trial sponsored by the makers of Galantamine. The mean MMS use score in this trial was 15, indicative of moderate dementia. This trial reported no differences in measures of daily functioning, cognition, behavioral disturbances or caregiver burden.

Next slide...a second open label, head-to-head trial compared Donepezil to Galantamine over 12 weeks. Although patients in this trial were considered to have mild to moderate dementia as in the 52-week trial, the mean MMS [Inaudible] score was 21 out of 30 indicating more mild impairment. This trial was funded by Pfizer, the makers of Donepezil. Significant differences favoring Donepezil were reported for measuring daily function, cognition and physician and caregiver satisfaction. The measures used in this trial [Inaudible] showed up in a number of trials where [Inaudible] and I wanted to point out that we were unable to determine if this measure had previously been validated.

Next slide...a single 12-week trial compared Donepezil to Rivastigmine. This trial again was funded by Pfizer the makers of Donepezil and its design was similar to the 12-week trial comparing Donepezil and Galantamine. Included patients were characterized as having mild to moderate disease although again the mean base find MSSG score of 20 is indicative of fairly mild impairment. Results at this trial indicated no differences in cognition at 12 weeks, but Donepezil was significantly better than Rivastigmine on measures of physician and caregiver satisfaction. Again, this is the same type of [Inaudible] measure that I mentioned in the previous trial.

Next slide...general evidence of efficacy and effectiveness of the included drugs comes from 20 placebo-controlled trials and 7 systematic reviews or meta analyses. Only one of these trials was considered an effectiveness trial. The remaining 19 placebo-controlled trials were considered efficacy trials. I'm going to just review a portion of this evidence here. The only effectiveness trial...I'm on the next slide...was the AD [Inaudible] study, which followed 565

patients randomized with Donepezil or placebo over three years. The primary outcome measure in this trial was the Bristol activities of daily living scale. At three years significant differences between Donepezil and placebo were reported on the Bristol ADL and the MMSE. Although statistically significant, these differences were clinically modest. There were no differences in progression of disability or the rate of institutionalization.

Next slide...one pooled analysis, placebo-controlled trials, three cholinesterase inhibitors were identified. This analysis included Donepezil, Galantamine and Rivastigmine. The results reported in these meta-analyses represent that the pooled effects of these drugs as a class and did not make indirect comparisons. Global responders were defined as those that did not get worse on global outcome measures such as the PDXE or the civic plus. Cognitive responders were those that showed improvement in cognition defined as a four or greater point improvement on the A [Inaudible]. The number needed to treat...to yield one additional cholinesterase global responder was 12, and the number needed to treat to yield one [Inaudible] cognitive responder was 10. Compared to the placebo 8% more of the cholinesterase inhibitor treated patient reported an adverse advent. Eight percent more dropped up, 7% more dropped out because of adverse advents. Although this analysis provides a general [Inaudible] for the three cholinesterase inhibitors as a class, we did not identify any evidence that included all drugs reviewed in this report.

Next slide...I'm not going to present any other general evidence although you can find a detailed discussion of this evidence in the report. One particular aspect to know is the discussion of functional improvement measures and also of behavior. For approval, the FDA requires a measure of cognition such as the AD cog and the measure of global response is the CGIC or the civic plus. In Canada and Europe I've been told that a measure of functional improvement also typically is required. In the draft report we spent significant attention focusing on outcome measures such as cognition, global response, functioning and behavior where functioning and behavior may actually track a little bit better with disease status and real population.

Next slide...the question of time to response and time required to assess clinical response is difficult to answer given available evidence. Comparative evidence is insufficient in quantity and the timing [Inaudible] measurements used in the three trials we identified was inconsistent. We attempted to evaluate time to effect and time required to assess clinical response using placebo-controlled evidence, but in the end the trials were too heterogeneous in design and timing of the assessments for us to draw conclusions about one drug compared to another. What I mean by that is assessment time points and the measures used to assess the particular aspect of the treatment were not always the same and we were hesitant to compare trials to assess that one, two and four works for a trial that assessed at two, four and six weeks. Furthermore, the issue of statistically significant differences compared to clinically significant differences is problematic for Alzheimer's disease. Because it is progressive in nature the time to effect [Inaudible] response is dependent on base one disease severity. Additionally, the ability of placebo-controlled trials to detect statistically significant response is dependent on sample size where large trials may identify significant differences earlier than smaller trials. Clinical response is difficult to assess given that no standard definition of a clinically significant difference exists not to mention the issues already mentioned. Our conclusions regarding the essence for time to response are more completely summarized, again, in the full report.

Next slide...for tolerability and adverse events some evidence is provided by the three open label head-to-head trials. Although distances may be real, relative [Inaudible] and adverse effect support withdrawals and withdrawals because adverse events appear to be more consistent with the trial sponsor than with the drugs examined. For instance, trials sponsored by the makers of Donepezil consistently demonstrated trends and adverse event reports and withdrawals favoring Donepezil over the comparator. [Inaudible] sponsored by the makers of Galantamine showed insignificant differences favoring Galantamine when any differences were noted. Comparing drug trials however, the relative instance of adverse events report withdrawals... withdrawals because of adverse events was quite variable.

Next slide...using placebo-controlled evidence we pooled trials to calculate the mean incidence of some specific event. In some trials authors did not report all adverse events. They may have only reported events that occurred in less than 10% of patients and I have indicated not reported where this applied. We point up two trials from Memantine although one of these trials randomized patients already stabilized with Donepezil, which could compound the results especially for adverse events. One important consideration when interpreting the table here is the [Inaudible] intervals. The message of assessment and range of recorded events was quite variable across trials. These figures should be interpreted with caution. That said, general trends provided by the table indicate the highest incidents of GI related adverse events for Rivastigmine. We did note, however, in these trials that the titration schedule generally was faster than that currently recommended and some trials you type doses than those seen in clinical practice today.

Next slide...[Inaudible] have practiced these stems from one meta analysis and four placebo-controlled trials for Tacrine. This evidence consistently suggests higher rates of hepatotoxicity for Tacrine treated patients. As many as 52% of patients in placebo-controlled trials had elevated liver enzymes. Similar evidence was not found in trials of Donepezil, Galantamine, Rivastigmine and Memantine.

Next slide...for gastro intestinal [Inaudible] and loss of body weight I focus here on comparative evidence. One long-term trial...in the one long-term trial no differences were found between Donepezil and Galantamine although the shorter trial, the 12-week trial reported higher rates of gastro intestinal side effects for Galantamine. In the 12-week trial comparing Donepezil to Rivastigmine, more gastro intestinal adverse events were reported among the Rivastigmine treated patients compared to the Donepezil treated patients. Although this evidence is consistent with our pooled estimates from placebo controlled trials, I will again point out that these trials appeared to be bias in the direction of the sponsor. We did not identify any comparative evidence that specifically addressed loss of body weight.

Next slide...based on available head-to-head evidence, no differences in cardio vascular events were noted between Donepezil and Galantamine and Donepezil and Rivastigmine. Placebo controlled trials revealed no significant differences in cardio vascular events, vital signs or UCG(?) findings.

Next slide...overall no control trial compared the efficacy of Alzheimer's disease drugs in a sub group to the efficacy in the general population. I will summarize a few studies that we identified for some of these sub groups.

Next slide...one sub group analysis of pool data from four placebo controlled rat [Inaudible] trials conducted an analysis by age, race and sex. Opposite of this analysis reported significantly better cognizant response among patients older than 75, but no differences were noted by race or sex. Other evidence we identified was inconclusive.

Next slide...no trial compared a population with Parkinsonian features to a population without Parkinsonian features. In general, trials that did not exclude patients with Parkinson's disease or features of Parkinson's disease would build similar effect (inaudible) to those noted in trials that did exclude [Inaudible] patients.

Next slide...similar trials compared population with [Inaudible] vascular dementia to a population without vascular dementia. We did identify one sub group analysis that recorded large excrement differences between Rivastigmine and placebo patients with [Inaudible] vascular dementia. However, other evidence was insufficient to draw conclusions about one drug compared to another.

Next slide...evidence for the effect of Alzheimer's disease drugs on patients taking other commonly prescribed drugs or visa versa is insufficient. In the full report we summarized known pharmacokinetic properties that may influence prescribing or patient monitoring, but this evidence is not derived from published evidence. It is simply a summary of information provided to the FDA.

Next slide...so overall the bottom line is that there is no double blind comparative evidence for drugs used to treat Alzheimer's disease.

Next slide...open label evidence is limited to the comparison of Donepezil with Galantamine and Donepezil with Rivastigmine. Results are inconsistent across trials although Donepezil was favored in two short-term trials. Short-term here meaning 12 weeks. The only long-term trial found no differences between Donepezil and Galantamine.

Next slide...more specific adverse events the highest rate of GI [Inaudible] adverse events was reported for Rivastigmine. Donepezil may handle lower incidents of GI related events than Galantamine although a long-term comparative trial found no differences. Conclusive evidence suggests that Tacrine presents a substantial risk of hepatotoxicity.

Next slide...evidence is insufficient to draw conclusions about the time to effect, their differences in efficacy or adverse events for these drugs and sub groups.

Next slide...that's it. I'm happy to answer any questions or provide clarification on anything that I presented.

Daniel Lessler, M.D.: Thanks a lot, Rick. Actually, first thing I was going to do is open it up to the committee members to address questions to you. How long are you available, Rick?

Rick Hansen: I cleared my calendar until 2:00 although I believe I was told until 1:00.

Daniel Lessler, M.D.: That's just helpful to know just to have you hang on the line as we go through discussions. But right now I was just going to open it up to see if there are any members of the committee that have specific questions for Rick on his presentation. Jason, are you there? Were you able to follow along?

Jason Iltz, Pharm. D.: Yep, I have everything pulled up.

Daniel Lessler, M.D.: Great. So...

T. Vyn Reese, M.D.: I'm Dr. Reese on the committee and one of the concerns I had is the weight loss issue, which in clinical practice it can be significant and the patients don't complain of it. The evidence sounds like it is very, very sparse in that area as to whether there are any differences in these drugs in weight loss, which is basically another manifestation of GI(?) toxicity. Sounds like, from what your view says, there really is no discernable difference or no trials that really tell us that there is any difference in this specific area. Is that true?

Rick Hansen: That's accurate. We did search with a specific term of weight loss with each of the drugs, but what we ended up doing though was going to each of the different trials and because of the methods of assessing adverse events it's so variable with very few using standardized questionnaires it's difficult to say whether one drug has a higher rate or simply just assessed it more frequently.

T. Vyn Reese, M.D.: A similar side effect is nausea and vomiting. There are significant differences in the drugs in nausea and vomiting. Is that correct from your presentation?

Rick Hansen: That's correct but again I will just note the caveat that in some like for instance in Rivastigmine trials there were several that had a higher rate where they did use a faster titration schedule than what is currently recommended. If [Inaudible] a little slower, it may not be as bad.

T. Vyn Reese, M.D.: But the titration rate takes you a longer time to get to effective dose. That's the other side of the coin. Right? If you titrate slowly then it is a much longer time to get to an effective dose of the drug.

Rick Hansen: That's correct.

T. Vyn Reese, M.D.: But the GI toxicity may be less?

Rick Hansen: Correct.

T. Vyn Reese, M.D.: All right, thank you!

Jeff Thompson, M.D.: This is Jeff Thompson from Medicaid. Just on the weight loss issue a little tangential but we are looking at medical nutrition. There is a state-wide initiative to assess whether the medical necessity of meals in a can, the Ensure like products, central nutrition. I do have a concern that we are seeing quite a bit of BMI's that are less than 18 in these populations as we assess the medical nutrition in both home care and residential care. So I can tell you that what we're going to do is probably add this to the sheet of looking at whether these drugs might be contributing to that failure to thrive issue. So it is concerning a number of people out of BMI of 12 in home care and residential care. So we'll be taking a look at that.

T. Vyn Reese, M.D.: This is Dr. Reese again. The problem is these patients often won't complain and a caretaker will notice they are not eating and unless you are conscientious about weighing them you might not notice a significant weight loss, which in clinical practice in my, you know, my anecdotal evidence in my own practice I've seen this happen several times where weight loss can be significant with these drugs.

Jeff Thompson, M.D.: And we are monitoring weight loss as one of the indications of failure to [Inaudible]. Could I ask just a question? Given the high number of intention to treat, which is 1 to 10 and the high number of adverse events, did the reviewer have any sort of suggestions on the prudence of monitoring them with standardized questionnaires rather than clinical impression of responsiveness?

Man: Just to clarify, Jeff, you're talking about the number needed to treat...I think that's the number you...the number needed to treat, which is one in ten.

Man: Rick, did you get that question?

Rick Hansen: I'm not sure if I got it completely.

Jeff Thompson, M.D.: With the high number needed to treat a one to ten ratio and the high number of adverse effects with this drug class, does the reviewer see the evidence to think it is prudent to use standardized questionnaires in monitoring the effectiveness for efficacy of treatment?

Rick Hansen: If I understand your question correctly...in clinical practice it's my understanding that typically you don't use any of the questionnaires that are used in the trials. So in other words there is a gap between the evidence as far as how these patients are assessed and [Inaudible] and how they actually present in clinical practice. Is that getting at the point that you're making?

Jeff Thompson, M.D.: Yes, and then just that, you know; only one is going to benefit from ten treatments. And so then two actually monitor in a pre-posed using the standardized questionnaires that are used in the evidence to actually say, "Is this drug effective so that we both increase the effectiveness or efficiency and decrease the harm."

Rick Hansen: I think it's a valid point and I'd actually love to see it done. Using some of these assessment scales in clinical practice though...I'm not certain of the feasibility. What we did do

is because cognition and global change seem to be more important early on than the more severe disease...things like daily function and behavior seem to be easier to assess. We focused on those two aspects and what we did was we calculated a standardized [Inaudible] for how people respond on function skills and that standardized effect size was right around...between .2 and .3. So just to give you a short way to interpret that...an effect size of somewhere around .2 is considered minimal, .5 would be moderate and somewhere around .7 to .8 a very good effect. So on those measures that I think are a little easier to assess in clinical practice we're showing very minimal effect.

T. Vyn Reese, M.D.: Thanks. In clinical practice...this is Dr. Reese again; it's usually behavior changes that the caretaker is most aware of and will give you feedback on and that's often what guides the practitioner as to whether the drug is effective or not. And that's a very soft pinpoint as you all know. For the caretaker it can be a very important end point.

Man: Any other questions from the committee for Rick? If not, we'll open it up for stakeholder input and again I want to ask that people limit their comments to three minutes. As well, if I could ask that...just for each manufacturer if there is just one person from the manufacturer to speak to a specific topic rather than having multiple providers from the manufacturer. If there are multiple people from a single manufacturer...if somebody is here as well with sponsorship from the manufacturer, that's fine, but we're just trying to sort of be as efficient as we can here.

It looks like...one, two, three...five people signed up to speak to these medicines. Again, if you could identify yourself and whether you're with the manufacturer or receiving any sponsorship that would be appreciated. First is Dr. Wornell. Again, Rick, I would appreciate it if you can stay on the line just for this part. Are you there?

Rick Hansen: No problem.

Man: Okay, thanks.

Doug Wornell: Thank you for having me today. I'm Doug Wornell. I'm the Medical Director of the Geriatric Psych Unit at Auburn. I'm a Geriatric Psychiatrist. My entire practice is dedicated to dementia and Alzheimer's disease and I'm more than likely here because of my clinical views. I have a lot of experience with all of these medications. I speak regionally and nationally for all of the manufacturers of these medications. I am here today as a paid consultant by Novartis to say some words about Rivastigmine, but I would say I would be surprised if certainly in the treatment of the early disease if there is not a greater than one in ten response from all of these medications in early disease I think what you're probably more focusing on is moderate and more severe disease particularly now in light of the issues of the A typical anti-psychotics and the needs to try and reduce those because of warnings about lack of FDA approval and increased mortality with those medications the physicians in the community who see me as one of the thought leaders on this issue are coming to me and saying, "What can we do to limit those medications?" And there are certainly a lot of data with Rivastigmine to suggest that it will be one of those medications that can help to reduce the amount of other medications that has been shown in several large studies at UCLA and elsewhere, as well as...and probably related to that limiting the amount of whole myriad to psychiatric symptoms from anxiety to

psychosis and mood instability. That has been my experience as well with this medication. When I speak about Rivastigmine I hear a great amount of feedback from families and caregivers about more than any of the other medications about what the company is called super responders or powerful responses by other companies...the people who actually improve although you are well aware that for the most part the...a lot of the efficacy is hard to measure and delay of the progression of the illness is probably the standard of what has been measured in the studies. I would argue that one of the measures that is used in the study...the mini mental status examination is used in clinical practice and it is very clear to me that the mini mental status examination can stabilize with this medication.

I want to make one comment about the side effects. Rivastigmine has been shown in studies to have an increased amount of nausea and vomiting relative to the others. That, without question, in my mind is related to two issues. One is the titration issue. Two weeks is too quick to titrate Rivastigmine if those titrations in my practice are changed to a monthly increase there has been no difference between the various cholinesterase inhibitors as I see it. The other issue is the absorption of the Rivastigmine is quite rapid. You get a huge cholinergic load on the body if given without food so Rivastigmine and frankly all the cholinesterase inhibitors should be given with food. If you account for those two factors in my practice there has been no difference in the side effects. Thank you.

Daniel Lessler, M.D.: Next is Dr. Andrew Weiss. I'm sorry, Dr. Wornell you're signed up twice.

Dr. Wornell: This is as non-paid consultant for Forrest. They asked me to say a couple of words about Memantine. Is that okay?

Daniel Lessler, M.D.: It sounds like you are going to speak to a different agent so that would be okay.

Dr. Wornell: The reason for that is, and I want to speak about it as an adjunctive agent. This would be the only medication of the group that you have seen today that is used adjunctively with the others, which makes it unique in that way. Its pathway and clinical mechanism of action you're probably aware is different than the cholinesterase inhibitors. It utilizes the glutamate system—a completely different mechanism of action. So it would provide for these patients in long-term care. A dual mechanism of action and I think if you don't have...I could provide you with the studies with the severe impairment battery. The use of Memantine particularly with Donepezil, but I think the other cholinesterase companies have data as well showing quite a bit of improvement over mono-therapy in pretty much the standard now a days as patients reach the moderate stage of dementia and advance into severe diseases, which is when you see a lot of psychiatric symptoms. Pretty much the gold standard if you want to have a sense of doing everything you can relative to these medications is to use adjunctive treatment. Thank you.

Daniel Lessler, M.D.: Rick, are you there?

Rick Hansen: Yes, I'm here.

Jeff Graham, M.D.: I was wondering, you know, in the written review that we have included comments from you folks about Memantine and I was wondering if you would just offer your perspective from the standpoint of the findings of, you know the structured review you all did.

Rick Hansen: Sure, there is one published study that made our review and that was the Tariot 2004 study where patients already stabilized on Donepezil were randomized to additional Memantine and in that finding, again, these were moderately to severely ill patients. They were dementia patients and they did find significantly slower decline in cognitive and global assessment scores for those on Memantine. Although Memantine alone it's difficult for me to assess how severe those changes were given Memantine alone did significantly better than placebo in the only other trial we identified. We didn't identify any other trial. The reference was made by Dr. Wornell about other studies comparing Memantine as adjunct with other drugs. If that data is available we were unable to identify it in the published literature.

T. Vyn Reese, M.D.: This is Dr. Reese. Could I ask you some additional questions about Memantine?

Rick Hansen: Sure.

T. Vyn Reese, M.D.: The problem with Memantine is...one of the problems is dosing and the manufacturer recommends decreasing the dose in moderate renal insufficiency. Almost all...the vast majority of patients who we use this drug on do have moderate renal insufficiency, but they don't mention what dose to use. And then also the other problem is in severe renal insufficiency it's contraindicated because it's renally excreted. Is there any study anywhere about what dosage to use at different GFR's or is this totally a black box?

Rick Hansen: Not that I'm aware of Dr. Reese.

T. Vyn Reese, M.D.: All right.

Daniel Lessler, M.D.: Thanks. We'll continue here. The next is Dr. Gross.

Dave Gross: Good morning. Thank you Dr. Lessler and members of the committee for having me here today. My name is Dave Gross. I'm a clinical pharmacist employed by Pfizer Pharmaceuticals and I'm here on behalf of Aricept. Patients with Alzheimer's, as you know, are typically on multiple different medications for multiple different disease states just because of the population that they are in. And one opportunity that we have to lessen this burden for both the patient and mainly for the caregiver is Aricept, which is dosed once daily and can be started out at the lowest efficacious dose from day one. That's the 5 mg dosage form. Aricept is the only acetyl-cholinesterase inhibitor that falls into that category that you start out with an effective dose of 5 mg and it only takes one titration to meet the maximal efficacious dose of 10 mg.

One thing that I wanted to do before I came here was look at the specific data for our Medicaid population in the state of Washington so I went to the CMS web site and looked at our utilization in this state for the medication population.

Memantine is about 13% and Galantamine is about 8%. And Memantine is probably mostly used as we heard before as adjunct therapy to those who are already on an acetyl cholinesterase inhibitor.

More importantly, I looked at what dosages were being used in this population and we talked about the ease of titration with Aricept and looked at some of the studies where we had some side effects with rapid titration of other drugs and some of the other drugs take a long time, 2 to 3 weeks between each dosage, 4 different dosage forms until you get to the maximum dose. Well, in the State of Washington 69% of the patients on Aricept, and this is Medicaid population in Washington from the CMS web site, 69% of the patients on Aricept are on 10 mg. 17% of the patients on Galantamine are on their maximum effective dose and 15% of those on Rivastigmine are on their 12 mg per day dosage. What that tells me is that in our population of Medicaid patients here in this state we're not reaching maximally effective doses with the other acetyl cholinesterase inhibitors where in two-thirds of the patients on Aricept they are on 10 mg; the other one-third is on 5 mg, which is an efficacious dose. So it may be a tolerability issue. It may just be the difficulty in escalating the doses of the other medications, but this is our true data, which when you are comparing efficacy and scientific studies they are maximizing the doses and when you are comparing it in the real population here I don't...there's the disconnect.

The last thing that I would like to bring forward is that Aricept is now available in an oral dissolving tablet formulation, which for those of you that know that work in long-term care facilities and work with elderly patients, work with care givers that treat these patients that is beneficial for these people who have difficulty with swallowing. So I kind of took a different slant on this, but I really wanted to look at the real, live data in the State of Washington and bring that to your attention if you didn't know that. I appreciate your time and if you have any questions, I would be happy to answer them.

Daniel Lessler, M.D.: Thanks. Next is Dr. Elise Conlee.

Elise Conlee: Good morning. My name is Elise Conlee and I'm a science and research liaison working for Arthur McNeil Neurologic. Thank you for the opportunity to present to the committee this morning on Galantamine. I have some new information that has come out since the compilation of the OHSU systematic review. Galantamine, while remaining the same molecule has both a new name and a new formulation since then.

Galantamine was formerly known as Reminyl. However, there were prescribing errors made confusing Reminyl with Amaryl, a glucose control agents. Because those prescribing errors were potentially life threatening we decided to agree to a name change and the name chosen with Arthur McNeil Neurologic and the FDA is Razadyne. Razadyne is available both as the immediate release formulation that you all are familiar with in the past is Reminyl, but it is also now available in a new formulation, Razadyne ER and that is the extended release formulation. Again, the molecule is the same as before with Galantamine, however there is a new rate controlling membrane around the molecule. This membrane is independent of gastric pH and allows for a once-day 2D dosing of the drug.

Pharmaco-kinetically Razadyne ER is equivalent in serum and the area under the curve for the immediate release formulation. As one might expect with an extended release version there is a slightly lower Cmax and delay to the Tmax for the extended release version versus the immediate release. In order to look at clinical equivalency of the ER formulation versus the immediate release they did a study looking at 971 patients divided into placebo immediate release and extended release groups and in that the IR and ER formulations showed equivalent efficacy to each other and superior to placebo on measures of cognition and activities of daily living. So then they looked at tolerability and again there was no difference between the ER and IR formulations intolerability in the study. If anything there was a slight trend towards better tolerability for the ER formulation in the 24 mg dose. So in summary we see that it is...not only does Galantamine have the new name Razadyne, it has a new formulation Razadyne ER, which confers equal efficacy and tolerability as Razadyne IR but with the added convenience of once daily dosage. So if there are any questions, I would be happy to take those. Thank you.

Daniel Lessler, M.D.: Thank you. Okay, based on the sign up list I have here I think that is all for the people who requested...I'm sorry, did I miss...did you want to comment? Why don't you come up and...?

John Phillips: Thank you. My name is John Phillips. I'm a pharmacist with Evergreen Pharmaceutical. I have no sponsorship. In my practice study the majority of the patients have severe Alzheimer's, therefore the majority of them are on Memantine. With regards to mild and moderate Alzheimer's when I reviewed the literature I also could not find a clear cut leader. Therefore, I defaulted to prescribing tendencies. This tended to signify Donepezil and Rivastigmine with an advantage point to Donepezil possibly due to the once-daily dosing and also decrease in titration needed and also the adverse side effects. As seen by Richard's slide patients were withdrawing from studies due to adverse events. I can say that what I have seen occasionally with Memantine is usually they go 10 mg b.i.d. Some physicians have opted for 10 mg once daily even though it is not on the prescribing package insert. I would say maybe 2% of the patients I'm seeing this and it is just recently becoming a trend. Thank you very much.

Daniel Lessler, M.D.: Thank you. And so...is there anyone else who wanted to comment on Alzheimer's who might not have had a chance? Okay, what I think we will do now is open it up to some discussion amongst the committee. You know, I think the way we have worked this over the last few meetings we have had where we don't immediately jump to try and formulate any kind of motion. It's helpful, but perhaps just beginning with some comment on observations that people might have.

T. Vyn Reese, M.D.: Some of this is fairly easy and some is more difficult. Tacrine is a drug that is hepatotoxic and so we can cross it off. Right? So it's not used much anymore. The other drugs are much safer. So that clearly is a drug that is out. Memantine is really a different class of drug and is used in somewhat of a different way so it really doesn't fit with the other three that are left. And then the question is GI toxicity, which I think...there are differences and I think that we need to perhaps focus in that area of GI toxicity as one other way to make our decision. However, the results aren't persuasive given that the GI toxicity seem to vary given who sponsors the trial. So it's quite a challenging area. That's sort of like what I look at as what we know about these agents. The dosing frequency is...it's easier to titrate Donepezil and it's easier

for the physician to adjust the dosage and you get quicker to an effective dose so that is true. It's a definite advantage though it's not...it doesn't speak to the efficacy or other issues. Anyway, that's sort of my nutshell take on these drugs and I'd be interested in other people's assessment.

Patti Varley, ARNP: This is Patti Varley. It's interesting because as you were saying your comments I looked at the notes I had made during the presentation, which sort of matched that. I think for me the big question has to do with the data in relationship to the GI side effects and how to interpret that accurately.

Man: I'm wondering, as well, just given your specific experience in geriatrics and as a geriatrician whether there is a need from your standpoint to have multiple potential medicines available to start a patient on. I think that probably one drug would be nice to...I use these drugs every day so that's why I am so talkative about them and I use them all the time. So the question is I think probably you could start with one and then if one drug could be the preferred drug and then providers can switch. Now it's true the vast majority of people in the state who have this illness are on Donepezil so that may be...that will definitely effect what we do. I mean what providers have to do. Lots of patients may be switched if we decide that we wanted to put a different drug on. So that's another thing to think about. They have the market share right now. And actually at this point actually, Jeff, I want to turn to you for the record and again in terms of...from MAA...Medicaid's standpoint...

Jeff Thompson, M.D.: Why are you always picking on me?

Man: Yeah, I'm sorry. Well, I think if it helps that you...if you would reiterate how it works if a drug is not on the list, you know, listed on the PDL what that means in terms of access for...potential access for a prescribing physician. In other words is it still possible to access medicines that aren't necessarily on the PDL?

Jeff Thompson, M.D.: I think starting from high to low if there is a federal rebate Medicaid, you know, has to allow that to be, you know, as a drug that is available to Medicaid clients. Medicaid has no formula [Inaudible] so there isn't a "do not cover" sign on any medication as long as it is a federal rebate. Now that said within the PDL process, obviously endorsing status and DAW apply to any drugs that are listed on the preferred drug list. So if you are an endorsing provider and you write DAW you can get obviously a preferred or non-preferred drug. And then if you are a non-endorsing provider the DAW does not apply and you must call and ask permission. That was my question to ask you looking at the safety issues, you know, just getting some general guidance about how to, you know, improve the safety and efficacy of these drug classes and I'll just push that every time we have a drug class. Now I guess the nuances if you were to indicate that you do not want this on the PDL or have special directions we have to sort of talk about that in directing both Medicaid, the UNP and L&I as the special directions as it relates to safety and certainly we could discuss that. Did I error in any way, Jeff? I'm getting pretty good at this, aren't I?

Daniel Lessler, M.D.: Right. I think it's always important to underscore. Yeah, Patti?

Patti Varley, ARNP: This is Patti Varley. I want to clarify a point and that is with this recommendation it doesn't necessarily switch everybody who is currently on an agent and it would be for mainly new starts, or am I incorrect?

Daniel Lessler, M.D.: [Inaudible] is not part of the refill class.

Jeff Thompson, M.D.: That's correct. It would be if a patient is on a drug that was not listed as preferred. If it was a non-preferred and the prescriber was not an endorsing practitioner and did not write DAW it would be substituted at that time.

Jeff Thompson, M.D.: And I think that goes to your recommendations around the therapeutic interchange apply in this class and that you should direct specifically in your recommendations. I don't believe Medicaid is inclined to, you know, create disruption and move patients around in their medications specifically in this class, however, that said I am very concerned looking at the safety and efficacy of this class related to the medical nutrition that we're seeing now in the state related to also a number of dosing errors, titration errors, and other things that I think we do need to attend to, but...I look to your direction on that.

T. Vyn Reese, M.D.: This is Dr. Reese again. Number one, you can't substitute these drugs from one to the other. They are impossible to do. That's one right off the top. Number two is although they are very modestly efficacious you can't not have them on the formula.

Jeff Thompson, M.D.: There is no formula.

T. Vyn Reese, M.D.: Well, I mean...they can't be on the preferred drug list. Okay? They have to be drugs that we recognize and...for this patient group. So I think that they need to be drugs that we consider and evaluate for preferred status.

Duane Thurman: I don't know if I can clarify things or make them worse, but this is Duane Thurman. In terms of addressing Patti's question, depending on how you do this if you put the drug on...if you pick a particular drug and make it the preferred drug that will tend to shift...it has the possibility to shift. I don't know that that is something that's within what you should be considering in terms of, you know, that's not really a clinical, you know, evidence based situation, you know, once we do the cost analysis or something the shift may or may not occur. But if you're an endorsing provider you can write dispenses written and you will get the drug that you want. If you are a non-endorsing provider and you pick a particular drug for the preferred drug list, there will be some therapeutic substitution. So I think if you are leaning towards saying the drugs cannot be substituted or not similar than I think you have a choice of either saying it's not applicable, it's not appropriate to put it on a preferred drug list or you can call out and say that they all need to be on the preferred drug list and address any particular safety or other special population things to give direction as to how the agencies would then implement that.

Jeff Graham, M.D.: This is Jeff Graham. Although we did that on the second generation SSRI...or the second generation anti-depressants and SSRI's, we said they were not subject to therapeutic interchange within our program so what happens in that...we passed out this flow

chart for refills if someone prescribes a non-preferred drug it stops and has to get prior approval. If they are not an endorsing...or even if...I don't know if you know this on our refill thing, if a physician is endorsing and writes on the therapeutic...or substitution permitted, that can't happen. So it stops and either the pharmacist has to call and say it has to be a preferred drug or I have to...

Man: Stay away from the refill. That's the special category, of course.

Jeff Graham, M.D.: It is, but it's the same application once you say that it cannot be interchanged.

Man: I guess the difference would be if you're a non-endorsing prescriber you can still get access to whatever drug you want, you just have to go through whatever prior authorization criteria that Medicaid has set up. So there is access, but the distinction between having it on the PDL and not on the PDL whether you allow substitution or not is that endorsing providers would have the option to write, dispense and [Inaudible]. If it's not on the PDL there is the potential depending on how Medicaid sets things up that everyone will have to go through the PA process.

Man: Let me just give you a scale not in cost, but in utilization. We have approximately 4,000 clients on these drugs at this point in time so that gives you a scale of the utilization and I think Jeff is correct. We look at guidance around therapeutic interchange and that's at the pharmacy level. If you say no it doesn't happen and then the non-endorsing DAW applies for any preferred or non-preferred that you select.

Man: I was just going to summarize at this point and then maybe...and then maybe allow you to comment. It sounds like where we are at here is a sense that at least amongst the cholinesterase inhibitors we're talking about...there seems to be a consensus that they are of equal efficacy/effectiveness and I'm sort of trying to get the general gist of the group here that there may be some evidence that Donepezil is somewhat safer although it's soft, but it's certainly out there in published literature. And the third point is the sense that these medicines are not therapeutically interchangeable. So three things to consider as we move forward. Carol?

Jason Iltz, Pharm. D.: This is Jason on the phone. I just had a point of clarification that maybe Jeff could answer. Is every drug class that we review budget the therapeutic interchange unless we state otherwise?

Man: That is correct. Under the Senate Bill 6088.

Jason Iltz, Pharm. D.: Okay, thanks. One other thing maybe if Rick is still on the line. I just wanted to clarify; I thought he made a comment in relation to Dr. Wornell's comment where he was talking about there was some evidence out there that talked about maybe specific acetylcholine inhibitors that could decrease in the use psychoactive medication and the data came out of UCLA. Did Rick counter that by saying that was not published data?

Rick Hansen: I am still on the line and no, I did not counter that particular statement. I'm not aware of that data.

Jason Iltz, Pharm. D.: I guess my comment then would be if that data exists can we ask that it be forwarded to OHSU?

Man: I could see [Inaudible].

Rick Hansen: Is the question directed at me?

Jason Iltz, Pharm. D.: I think it was Dr. Wornell that quoted it so if he has that data can we just ask that he forward that to OHSU?

Doug Wornell: This is Dr. Wornell and I can see that that gets forwarded.

Jason Iltz, Pharm. D.: Thank you.

Doug Wornell: And, Rick, I don't recall, when is the next review for this drug class?

Rick Hansen: This is on a yearly update at this point.

Doug Wornell: Okay, thanks.

Carol Cordy, M.D.: Carol Cordy. I just have another question for Jeff. If a drug like Tacrine, which we're saying is not a safe drug...or is not a safe drug. It is on the list as successful to DSHS clients. Is that right?

Jeff: All drugs of the federal rebate are accessible.

Carol Cordy, M.D.: Okay. So there's no way we as a committee can limit what drugs...

Jeff: Well currently we have a PA on that drug, prior authorization, or just an [Inaudible]?

Carol Cordy, M.D.: I don't know if we have it on PA, but we don't have any utilization [Inaudible]. When I looked the last couple of years I couldn't find anything in our data that they were using it because there were the other safer...and basically if it wasn't preferred, you know, they would have to show...meet our PA criteria of why they need that drug, why is that medically necessary.

Jeff: So in effect if you give us a safety indication and new directives as a recommendation, you know, we can certainly caucus about whether that is a PA or an ETA, you know, or something like that. I look to you to guide us in that. That was the [Inaudible] to the question around, you know, the general efficacy of this class and it's use and whether, you know, I have to put on my other hat because, you know, with a number to treat at 110, you know, how do we know that we are getting the efficacy out of this class?

Carol Cordy, M.D.: And I guess the other question just stepping back...when we looked at other drug classes there have been studies that show that certain drugs are not efficacious or absolutely no better than placebo. Those drugs still will be accessible to client.

Jeff: As an example when you singled out Soma in one class we've been very successful in educating the provider community around its use and possible abuse and have taken down several thousand chronic users down to a number less than 50 and we just said, "Okay, you have been 20 years on this so you are getting diminishing returns." So you have been very successful in guiding us to better efficacy, better safety, better clinical practice.

Duane Thurman: I guess, this is Duane just briefly, the problem we run into here is as long as it is an FDA approved drug and they receive a Medicaid rebate on it, it is going to be available and the appropriate way to deal with it is through their PA process and to the extent you have comments that would assist them in doing that, that's what we need.

Man: Thank you. So are there any other thoughts now about this class of medications that people want to add? Inflecting on them? So would there...is there somebody bold enough to start by crafting a motion in terms of capturing the consensus here?

Man: I will. Just through comments earlier. The summary...the soft data we have looks like Donepezil is the least GE toxic. So that's one issue. Number two, Memantine is not in the same class as the other drugs and so it needs to be on there, too, but it can't be substituted so we're...and the other drugs really can't be substituted for Donepezil, but if Donepezil is not working or there is toxicity to it, the other drugs can certainly be used in a non-preferred drug way that we have used previously. So after considering the evidence of safety efficacy in special populations for the treatment of Alzheimer's disease I move that Donepezil and Memantine are safe and effective. This isn't really true...the next part...so I think we will delete that. These drugs cannot be subject to therapeutic interchange in the Washington Preferred Drug List for the treatment of Alzheimer's disease. So basically it is just Donepezil and Memantine.

Man: Does anybody want to take a look at that for starters? Just maybe think through sort of the implications, you know, understanding DAW and the PDL and therapeutic interchange here.

Woman: Did you say that you did not want them to say [Inaudible] risk factors?

Man: Evidence of...considering the evidence of safety efficacy in special populations for the treatment of Alzheimer's disease I move that the two drugs you mentioned are safe and effective.

Man: Yeah, that's right, delete that.

Woman: And interchange?

Man: Donepezil and Memantine cannot be subject to therapeutic interchange in the Washington Preferred Drug List for the treatment of Alzheimer's disease. It cannot be. They are not in the safe class.

Man: I believe that you should probably make that remain for the entire class and not just the two drugs—to give clarity to the pharmacists who are looking at a class specific interchange, not a specific drug interchange.

Woman: So the way it reads like this you would say that all the other drugs are subject to the interchange to Donepezil or Memantine, but Memantine would not be able to be changed.

Man: That's not...

Woman: That's not what he means.

Woman: That's not what you mean?

Man: No.

Man: I think you would say all drugs in this class are not subject to...

Man: All drugs in these classes cannot be subject to therapeutic interchange on the Washington Preferred Drug List. Cannot be for the treatment of Alzheimer's disease.

Man: Do we want to specify, you know, actually say cholinesterase inhibitors and MDA? That they are not...

Man: Right, cannot be...

Man: Can we just specify the classes?

Man: I'm just asking in terms of...just in terms of clarity.

Woman: The class [Inaudible] treat Alzheimer's.

Man: In this class, okay. If we do that...there are different classes of drugs in this class, but this is what the drugs are used to treat and we cannot substitute them.

Carol Cordy, M.D.: I have a question. Carol Cordy here. Why are you leaving out the other two—Galantamine and Rivastigmine?

Man: My reading of the data is that the data isn't great, but what data we have is pretty suggestive that it's less GI toxic at least in the studies that we have not...and it's not great data and some of it is faster titration mechanisms than other things, but what data we do have it looks to me that what little we have it is the least GI toxic and it is a big issue. GI toxicity is a big issue in this vulnerable patient group and I think that we, even though we don't have perfect data the data that we have I think is sufficient to be cautious and just to have this drug preferred—in my personal view. I mean I wish we had a perfect world, but we don't have enough data to be 100% certain, but it's enough data that makes me concerned that it is true.

Carol Cordy, M.D.: And I guess just in other drug classes that we've looked at we haven't necessarily put side effect profiles in the same category as safety. I mean there are many other drugs where the side effect profiles are quite different, but overall there is not strong evidence of safety.

Man: I think safety is really an important consideration and that's part of the side effect profile. Especially in a patient population where nutrition is paramount.

Carol Cordy, M.D.: I'm not disagreeing. I'm saying it's...

Man: That's my thinking. I will flush that out.

Patti Varley, ARNP: This is Patti Varley. I have a question having to do with the Soma example we had earlier and that is we have left Tacrine in there and just like the rest of them and we're talking about the fact that there is evidence of more [Inaudible] toxicity and I'm wondering if there is a way in here to do what we did with that example of Soma, which is to make it less accessible as a safety precaution and a protective mechanism.

Woman: You can say that you want that...just like you could say that a certain drug has to be included in preferred, you can say like in that case you want a certain drug to be included in those non-preferred. I think that's how you handled the Soma.

Man: Could we actually specify that we find Tacrine to be less safe than the other agents. I mean actually have that incorporated into the...

Jeff Thompson, M.D.: I think you can guide us as generic or as specific as you want. Obviously these are guidelines. The least specific guideline would be the...if we find there to be safety issues and...again, this is Jeff Thompson and we would recommend to the agencies to use prudence in allowing authorization. Or you can be very specific about it and we can take those recommendations.

Man: Well, you know, if we just call out the safety issue with respect to Tacrine and liver toxicity is that enough for agencies then to say, "We need to develop some guidelines or provider education around this and so forth,".

Woman: You could state something like take...you recommend that Tacrine not be on the Preferred Drug List due to safety concerns and that it be subject to either prior authorization or the drug of last choice or something in that nature, for treatment of this. Right now as it states basically it would...when we make the recommendation to the agency directors only Donepezil and Memantine would be considered. The others would be determined not to be preferred. As it is right now it would be considered a non-preferred drug or not eligible to become a preferred drug. Put it that way.

Man: Again, you can be as generic or as specific and if you are a specific that you want us, you direct us to use all efforts including prior authorization to limit its use to only medically necessary indications and we will do so.

Carol Cordy, M.D.: Aren't we also then putting the other two...the Rivastigmine and Galantamine in somewhat that same category by not...

Man: No, those would be a preferred...an endorsing provider writer DAW has access to all four of those medications. A non-endorsing provider writing without DAW who is preferred will get those medications. A non-endorsing even if DAW or not writing for the non-preferred it will stop and require prior authorization. The prior authorization we will work out after this. What you are doing indicates the Soma and not to beat up on Soma, but you are giving us additional instructions of how to deal with the safety issues.

Carol Cordy, M.D.: For Tacrine?

Man: For Tacrine.

Jason Iltz, Pharm. D.: This is Jason Iltz. I think that I agree with some of the comments that Carol and Patti are talking about. In the past when we have looked at this drug classes we've been tasked with making a statement about safety and effectiveness and so I think what we have right now is that we have really inadvertently kind of tied the hands of the department heads and potentially decrease choice. In the past what we've done is we've looked at the relative safety and effectiveness so in this particular case I would...at least my view of the data is that four of the five medications are at least relatively safe and somewhat effective and I'm excluding Tacrine from that. And then we've gone on in the past to make a statement that would say, "We would recommend that for example in this case Donepezil and Memantine be included but that wouldn't excluded the department heads from adding anything else and they may choose to add all of the medications, but as long as we have our choices on there as well, I think that's what is important and we don't exclude any inadvertently.

Man: I think that's a good point, Jason. So for example the motion would clarify that each of the...taking Tacrine out for a moment that each of these, Donepezil and so forth are safe and effective and then we would actually specify or recommend that Donepezil and Memantine be on the PDL.

Jason Iltz, Pharm. D.: Sure. And if you could say that we prefer Donepezil because there does appear to be some data that is less GI toxic and we would like that as potentially maybe available as a first choice.

Man: I think the problem with that might be that, you know if...I guess if we specify that Donepezil must be on there that would deal with the issue. Otherwise, I think the concern is that if for pricing reasons and so forth one of the other agents were less expensive and that was driving the decision if we had said these are equal in safety and efficacy then one of the others...where we have some concerns although they are soft, but there is published data around GI side effects might not be adequately taken into account.

T. Vyn Reese, M.D.: This is Dr. Reese. That was my concern in making the motion is that one of the others would be first...would be on the preferred drug list due to cost and that is how it would be...and that may be a disservice to our patients.

Woman: I think what Jason is trying to say and this is a point of clarification, I was going to ask, was the intent of your motion to say that Donepezil and Memantine should be on the preferred drug list as your recommendation or that we should choose between the two?

Man: They are totally different drugs so I'm not saying that they are different classes and they are different drugs so you can't choose between the two of them. They are like apples and oranges.

Woman: Okay. So what Jason...the way that Jason stated it if we said that they were all safe and effective and that the committee recommended that Donepezil in addition to Memantine or Donepezil in addition to one other agent or two other agents...

Man: That's fine.

Woman: Okay. And that way if you want Donepezil...you have done that before. If you want Donepezil on there then it would be on there and then we could leave it to the cost analysis to determine among the others, which would be on the list.

Man: Right. So if I could play with your motion here, Vyn. It would say I move that Donepezil, Galantamine and Rivastigmine and Memantine are safe and effective. Donepezil and Memantine should or must be included on the PDL and then I think if we could comment on Tacrine that we find Tacrine to be less safe than the other agents in this class because of increased liver toxicity and...what I'm hearing is that that would be enough guidance to...

Patti Varley, ARNP: A comment here. When we did the Staten class we named them all except Crestor. Remember that? So Crestor requires some special authorization. It's not interchangeable. It's all those kinds of things. It was such...I don't know, Jeff, if you think we are silent on Tacrine in this, don't name it in the class, but give you then that opportunity to do what you want to with that.

Man: Jeff, I actually want to clarify because I think the circumstances were different with Crestor in as much as the evidence around safety was concerned with much...it was much murkier. I think the evidence here with Tacrine is much more compelling.

Rick Hansen: I agree.

Man: Well, the other thing though is that it is important to put all the names in this so we have clearly like said that we should have the names of all those drugs in there.

Man: Nancy Henning?

Nancy Henning: Just one comment as I listen to Jason and I listen to Kevin. I think that what he said is that the drug is relatively safe and somewhat effective and I think that does reflect what your data is.

Man: So that...just sort of toning down the...so just modifying or qualifying safe by saying “are relatively safe and modestly effective”. Are you...

Woman: He said relatively and somewhat and I thought it also fit with what I heard and what [Inaudible] just said.

Man: I don’t know if we need to add that. Then we would have to do that with every class and change the thing. They are safe and effective and you’re right, it’s all relative.

Woman: I understand that it is all relative, but I have been sitting here listening to the evidence put out and some is more relative than others and some you want to tone down a little bit more and considering what he has said, I think that he captured more of what is going on here.

Man: But if it’s your relative even relatively effective is important.

Woman: But you make it sound like its more absolute [Inaudible] than effective, and I don’t think what the data shows. But it’s your choice.

Man: I would caution you to...when you start qualifying levels of...

Man: Right, I don’t want to put it in...

Man: But your point is well taken.

Man: Can I just make a point of clarification on the sentence that says that those two drugs must be included on the Washington State Preferred Drug List? All drugs are on the drug list. If you want them preferred...they actually should be included as preferred drugs. I know it’s a nuance, but it...they are all drugs...

Man: Okay, so it must be included as preferred drugs on the Washington State Preferred Drug List.

Man: Right. It’s better clarity.

Woman: As preferred drugs.

Man: This is still my motion so I should...after drug list Tacrine is less safe because of hepatotoxicity than the other drugs in this class and should not be included on the Washington Preferred Drug List.

Man: Considering the evidence of safety, efficacy and special populations with treatment of Alzheimer's Disease, I move that Donepezil Hydrochloride, Galantamine Hydrochloride, Rivastigmine Tartrate and Memantine Hydrochloride and safe and effective, period. Donepezil and Memantine are...hold it. It's misspelled. Donepezil is misspelled. Donepezil and Memantine must be included as preferred drugs in the Washington State Preferred Drug List. The evidence indicates that Tacrine Hydrochloride is less safe because of added toxicity than the other drugs in the class and should not be included as a preferred...drugs left out...as preferred...as preferred on the Washington Preferred Drug List, period. All drugs in this class, Donepezil, Galantamine, Rivastigmine, Tacrine and Memantine cannot be subject to therapeutic interchange on the Washington Preferred Drug List for the treatment of Alzheimer's disease, period. Does that capture [Inaudible]?

Group: [Inaudible].

Daniel Lessler, M.D.: [Inaudible].

Patti Varley, ARNP: This is Patti Varley and I will second that motion.

Daniel Lessler, M.D.: Great. Any further discussion or comment? All right. All those in favor say Aye.

Group: Aye.

Daniel Lessler, M.D.: Jason?

Jason Iltz, PharmD: Aye.

Daniel Lessler, M.D.: Thank you. Opposed [Inaudible]? All right, the motion passes. So, thank you. So next we're going to move on to an update on skeletal muscle relaxants.

Man: And Rick, you can leave the phone now if you'd like to.

Daniel Lessler, M.D.: Oh, Rick. Yes, thank you very much.

Rick: You're welcome. [Inaudible] do a good job.

Daniel Lessler, M.D.: Thanks. Take care.

Rick: Okay.

Man: I guess in my materials I don't actually...I mean, I reviewed the skeletal muscle relaxants...we don't have slides on it. There were no updates of slides because there was very little change...and so that's what I was going to say. By way of presenting an update, I think those of us who had an opportunity...those of us who had an opportunity to review the most recent update from working on the muscle relaxants would...I think my sense of it is that there

was nothing new or compelling. I'm actually wondering if in here we have the last motion made...

Man: We do.

Man: on this?

Man: Is it [Inaudible]?

Man: [Inaudible].

Man: On page 17 of the [Inaudible] review history...

Daniel Lessler, M.D.: [Inaudible].

Man: It's under page 17, though.

Daniel Lessler, M.D.: It's tab 3. So just to remind people, the last recommendation was that...can't pronounce this...

Man: Carisoprodol.

Daniel Lessler, M.D.: Carisoprodol. Thank you. Is subject to abuse and therefore is not recommended for the indication of spasticity; that Tizanidine and Baclofen are considered safe and efficacious for the indication of musculoskeletal indications that Methocarbamol, Cyclobenzaprine, Metaxalone, and Orphenadrine. That's where it got abbreviated was...did that say should be considered safe and efficacious?

Woman: Yes. Those were the ones that you said that were considered safe and efficacious.

Daniel Lessler, M.D.: Right. Okay, that's right. I recall. I'd ask you to present any other comments from the committee or sense that this should be changed in any way, based on the review. And, Jason?

Jason Iltz, PharmD: Yes.

Daniel Lessler, M.D.: I...so, I didn't know if you had any comment.

Jason Iltz, PharmD: Not at this time.

Daniel Lessler, M.D.: Is there...I don't have any stakeholders, I believe, who have asked to speak on this class, is that correct? No. Okay. That is correct.

[Inaudible]

Daniel Lessler, M.D.: All right. So, could...I'm wondering if somebody would be willing to make a motion maybe to the effect that our...could we just say that we don't want our previous...maybe we just want our previous recommendation to stand and that would be...will that do? Okay.

Man: [Inaudible].

Daniel Lessler, M.D.: Actually, because I'm...I was going to ask somebody else to...just probably not a good idea, process for me to do that.

Man: [Inaudible].

Daniel Lessler, M.D.: I think we're looking at it right here on...

Man: I think you could do something as simple as saying that [Inaudible] on evidence that you recommend no changes to the Preferred Drug List in this class.

Man: So moved.

Daniel Lessler, M.D.: [Inaudible] recommendation.

Woman: I just want to clarify. Do you want to say no changes to the Preferred Drug List or no changes to the recommendation? That's two different things.

Daniel Lessler, M.D.: The recommendation. That's what we can comment on. So, could I ask for somebody to make a motion? Maybe just...thank you.

Carol Cordy, M.D.: Carol Cordy. I move that we accept the previous recommendation as stated. I recommend that we accept the previous recommendations for this drug class without any changes.

Patti Varley, ARNP: Do we want to include...this is Patti Varley. That was after reviewing the updated information.

Daniel Lessler, M.D.: So after reviewing the updated information, comma, [Inaudible]. But except should be except. Okay is there a second?

Man: Second.

Daniel Lessler, M.D.: Thank you. Any further discussion? Okay. All those in favor say Aye.

Group: Aye.

Daniel Lessler, M.D.: Opposed [Inaudible]. All right. So this class is reviewed and I think now we, actually even a few minutes early have an opportunity for a break.

Man: Sorry.

Daniel Lessler, M.D.: Yeah.

Man: And we do have...Dr. Chow will be on the line at 11:00.

Daniel Lessler, M.D.: 11:00. So why don't we break until 11:00. Is that okay, John? If people could promptly come back at 11 because Dr. Chow will be on the line. Thank you. And we do have a presentation from the folks at the OHSU.

Man: Jeff, do we have...Roger, are you there?

Jeff: He's, probably in a couple minutes.

Daniel Lessler, M.D.: Couple more minutes. Okay. We'll we're going to...might be a bit premature. All right. So we're just expecting Roger Chow from OHSU to call in any second here. Eric, where are the slides for this? Are they in our packet? Oh, they're outside. Okay.

Roger Chow: Hello?

Daniel Lessler, M.D.: Hello.

Roger Chow: This is Roger Chow.

Daniel Lessler, M.D.: Roger, Dan Lessler here.

Roger Chow: How are you?

Daniel Lessler, M.D.: Fine, thanks. Thanks for joining us.

Roger Chow: No problem.

Daniel Lessler, M.D.: So, I think we're...we have...Jason, are you there?

Jason Iltz, PharmD: I am.

Daniel Lessler, M.D.: Great. Thanks. I think we've...oh, well, why don't we go ahead and get started. So we have your slides up here...

Roger Chow: Great.

Daniel Lessler, M.D.: and we're just looking at the first title slide and you can just go ahead and take it from there, Roger.

Roger Chow: Yeah, I'll just go quickly through 'cause I know I've presented similar slides the last couple of years. I'll try to focus on new stuff for this update. So, of course, I want to acknowledge the folks at the Oregon [Inaudible] that worked on this. Why don't we go ahead to the next slide? So that just shows the objectives we'll look at some very brief background key questions, results mainly is what we're going to focus on. Next slide. So for this update one of main changes was we redefined long-acting as anything that's given three times a day or less. Previously we had defined it as twice a day or less, but that excluded drugs like Levorphanol, which are often dosed three times a day. Methadone, of course, is often dosed three times a day, so that's why that change was made. A couple of other changes since the last update; long-acting hydromorphone was FDA approved in 2004. It is only FDA approved for Opioid tolerant patients who are already on moderate doses. It is not approved as a first line long-acting Opioid. Long-acting oxymorphone is currently undergoing the approval process, although when I last checked about a month ago it had not [Inaudible] approved. Population outcomes are unchanged from the previous update. We are looking at adult, not looking at HIV or cancer pain of course.

Next slide. So this just summarizes the key questions. We are looking at the comparative efficacy of long-acting opioids for non cancer pain. Basically three categories in comparisons, head-to-head trials, placebo controlled or active controlled trials. Trials of long-acting versus non-acting opioids. We looked at comparative safety and for safety we included observational studies. And then we looked at [Inaudible] information about comparative efficacy or safety of specifics of the population. None of the key questions have changed.

Next slide. This referred to the search strategies. We basically repeated the search strategies that we've done looking at three different electronic databases. We received pharmaceutical company permission, I believe, for Fentanyl and for Hydromorphone and Oxycontin, I believe are the three, but I don't have that at my hands, but I believe we believed three dossiers for this update. We also looked at reference lists and searched particular journals anything we got on [Inaudible].

Next slide. The data collection is completely unchanged and is the same for all of the [Inaudible], so I won't go into that. For the Opioid reviews, we really have been unable to do a meta-analysis because the study was so heterogeneous. The quality of study wasn't quite there for many of the drugs for comparison. And then the outcomes that are measured [Inaudible] varied quite a bit in terms of the tools used and how they are reported and measured for all the studies. So the comparisons have all been qualitative as were the previous updates before.

Next slide. So the main results in efficacy in terms of head-to-head trials of long-acting opioids, the three trials that we have here are the same three that we have for Update No. 2. There was a fourth trial published by the same author that did the trial of Transdermal Fentanyl vs. PO Morphine. We have received some feedback as a comment that that trial has been published. It was previously only available in abstract form. They said it has been published in spine. But we did searches in the journal, we did electronic searches and we still couldn't find it. So I believe that it is still unpublished, unless it has been just published in the last couple of weeks. But that was a trial from pairing Transdermal Fentanyl with PO Morphine. Nothing new to say about the head-to-head trials. The trial of Transdermal Fentanyl vs. PO Morphine was rated poor quality, mainly because it included many patients...it was unblinded and it included

many patients who had previously failed or been on PO Morphine. [Inaudible] but was a little bit better with Fentanyl and withdrawals were a little bit more frequent with morphine. The other two trials, one was a 1-person twice daily PO Morphine, that only showed that a once daily Morphine was better for one out of seven sleep measures, otherwise there were no differences for pain control. The third trial was a very small trial of chronic pain [Inaudible] and showed no differences. None of those trials were very good quality.

Next slide. So in terms of trials of long-acting opioids vs. [Inaudible] or non opioids, we have three new trials. All three new trials were in patients with neuropathy. We included a trial with Levorphanol, that we had previously excluded but, because we had changed the definition of long-acting opioid for this report, we included that trial this time. We also included the first randomized trial of Methadone, and there was a third trial of long-acting Oxycodone in a diabetic neuropathy, I believe. I just wanted to comment on the Methadone and Levorphanol trials. Both of those trials used a pretty unusual...or different, I should say, design. The Methadone trial gave people either active Methadone or placebo only every other day. So you would...you were randomized to either Methadone or placebo on one day. The next day they would measure outcome then you would get neither. And then the following day they would again randomize patients to either Methadone or placebo. So that design, obviously, does not reflect what most people do in clinical practice with Methadone in terms of only dosing once every couple of days and it's really hard to prepare those results with the other trials, which gave the long-acting opiates out continuously. The trial of Levorphanol was also different from some of the other trials in that they didn't feel that they could give these patients the chronic pain of placebo, so they considered low dose Levorphanol in the comparative group and high dose was the kind of the active treatment group. So they compared high versus low dose Levorphanol. Again, different from other trial designs that did actually use kind of inert placebo or true placebos. The trial of Oxycodone was similar to other trials and pretty comparable in terms of its design. None of the three new trials were found of good quality. They were all rated fair quality. Again, all of these trials looked [Inaudible] populations and intervention as well as the best outcome. Because they were all...they were not head-to-head comparisons, it also made it very difficult. We didn't feel that he could draw any conclusions about comparative efficacy in these trials, particularly from the Levorphanol and Methadone trials.

Next slide. No new data on long-acting versus short-acting opioid with same seven trials that we looked at previously. There are no [Inaudible] long or short-acting opiates.

Next slide. In terms of safety, head-to-head trials of long-acting opioids, only two trials were included; the third trial was a response trial was a very small trial of chronic pain [Inaudible] which really didn't [Inaudible]. And these trials had poor quality effort [Inaudible] assessment. So difficult to glean much from them. One of the studies did suggest constipation [Inaudible] with Fentanyl, though withdrawals due to adverse event favored Morphine. So...and withdrawals from adverse events, again, are also considered a surrogate for severe or intolerable [Inaudible] event.

Next slide. In terms of safety from studies of long-acting opioids versus placebo or non opioid, in general the quality of adverse event assessment was pretty poor in all of these trials the worst in the quality for efficacy, which already wasn't ideal. There were broad ranges for

adverse events for each of the long-acting opioids with overlap between all of the drugs, and there's no pattern that emerged as adjusting in increased safety for any of the long-acting opioids.

Next slide. In terms of long-acting opioids versus placebo or non opioids. Also we included observational studies here. And the two...I wanted to highlight these two retrospective [Inaudible] studies from the California Medicaid Population. These studies were performed by the same group and so they're related studies and maybe should be considered one study. But they looked at slightly different comparisons and slightly different populations. I think one was done later than the other one, so the numbers are a little bit different from one to the other. But it's essentially looking at the same population. And they found that constipation would increase with long-acting Oxycodone prepared with Transdermal Fentanyl, but there was no significant difference with long-acting Oxycodone prepared to...excuse me, with Fentanyl compared to Morphine. Now, this study...the biggest concern, I think, with this study is that there were really large baseline differences between other groups that received different drugs...I mean, patients who received Transdermal Fentanyl tended to be older, they tended to have different diagnoses. Even the gender and race breakdown was significantly different. So this makes you worried that there's some type of selection going on and that patient in one group may be getting the drug for other reasons that we can't measure. And we worry about this with all observational studies, of course. And we worried about this even when you don't see big baseline difference, that there are unmeasured [Inaudible] or biases that are taking place. That's why we always put more of a...more emphasis on randomized trials when we're looking at outcome. So when you see huge baseline differences between the groups, that's kind of another red flag. And that's why these studies were rated fair quality. We think they were done well, they actually tried to control for the things they could control for. But when you look at these baseline differences, it just looks like they're studying two completely different populations and people received these drugs for different reasons and we may not be able to capture all of that in the things that we're measuring and trying to control for. The other observational studies were not particularly helpful, they're the same ones that we looked at for the other updates and reports.

Next slide. There are a couple of other studies that we continue to follow. So it would be ongoing Drug Abuse Warning Network Study [Inaudible] mention through 2001. These are the more recent than we had reported for the last update. For the different opioids. [Inaudible] increased by 641%. Morphine by 113%. Oxycodone by 347%. The Drug Abuse Warning Network Study is done in ERs throughout the country and they basically report ER visits related to different drugs of abuse. The problem, again, with interpreting the data from a non study are that you don't have denominators for how many prescriptions are being given, and when we know the prescriptions for many of these drugs have also increased, the [Inaudible] have increased out of proportion for any of these, but specific [Inaudible] opioid. The other kind of difficulty of interpreting the DAWN data is that it doesn't distinguish short from long-acting opioids, so you don't know if the Oxycodone, for example, is a short-acting Oxycodone vs. long-acting Oxycodone. It also doesn't distinguish well whether the patients are [Inaudible] the drugs illicitly or whether these are patients that are getting them for legitimate, chronic pain. But I think the DAWN data is still useful for kind of looking up trends and we will continue to follow that.

Next slide.

Daniel Lessler, M.D.: Robert, can I ask you a quick question about the definition of ER mention?

Roger Chow: Yeah.

Daniel Lessler, M.D.: How does that...what...how do they decide what constitutes being mentioned? I mean, is it-...

Roger Chow: Yeah, it's a little bit vague, actually. The people are trained at these ERs. And so any time there's an intake, I believe, they have someone who's trained to kind of ascertain whether they think the ER visit is significantly related to an opioid. So I think there's some subjectivity there. But it also...I think they also incorporate urine tox-screens and things like that. So, there's a...they used to have a criteria to determine the link. But...and of course they train people at the different centers. That's probably as much as I can tell you about it. The DAWN study...there's a whole web site just devoted to the DAWN study where they have kind of pages and pages of data. And I actually am not sure how detailed they go into in terms of their message. But we can actually look into that some more, if that would be of interest.

Daniel Lessler, M.D.: Thank you.

Roger Chow: So the next line on other observational studies...so yesterday, actually, there was just an article in The Oregonian...it was either yesterday or the day before, where the State of Oregon has reported the number of deaths that occurred last year, and the numbers are either 96 or 104 depending on which method was used. So I think the health examiner reported a slightly lower number and then somebody who did some other type of analysis reported a slightly higher number. So it doesn't look like it's increased in 2002 at least, but it's still concerning because [Inaudible] deaths [Inaudible] with Methadone are high. I mean, they've increased since back in '99. Again, the increase since 1999 appears to be related to an increase in prescription, but, of course, there is a concern that, you know, Methadone has a potential because of its irregular half life and maybe provider inexperience, that if the [Inaudible] is broken that there is a potential for problem if people are converted to Methadone. So that's been a concern. And I think the message from yesterday's news report...I haven't seen that come out on the official Oregon website though, I'm sure it will pretty soon, is that at least the numbers of deaths haven't increased since 2002. I did see on the news report that they had done more [Inaudible] of the number of prescription. So my guess would be prescriptions since 2002 are about the same or have gone up. So, for what that's worth, we'll see what they have to say when they come out with their official report. There was also a case series of 96 Methadone associated deaths from 1992 to 2002 in kind of a [Inaudible] prescribing pattern. 15% were chronic pain patients. I think from all the...from both the State of Oregon and the Minnesota data what would be really helpful would be to see similar kinds of data on other long-acting opiates and try to figure out whether this increase in Methadone has [Inaudible] be seen with other long-acting opioids. And I haven't seen anything [Inaudible] yet.

Next slide. So this is long-acting vs. short-acting opioid safety. Again, the same seven trials that we've reported previously, no pattern suggesting that either long or short-acting opioids are safer.

Next slide. [Inaudible] populations. Really no new data to report on [Inaudible] populations. I [Inaudible] I should update this part of the bit. There's more data on neuropathic pain, but all the studies compare long-acting opiates to the placebo and don't really compare long-acting opiates to each other. So not able to tell whether one drug is superior or not to another for neuropathic pain. There continues to be almost no information on age, race or gender. People at high risk for [Inaudible] have generally been excluded from all of these trials.

Next slide. [Inaudible] what I just mentioned, a few trials that were excluded may be of interest. One was a head-to-head trial of Transdermal Fentanyl vs. long-acting Morphine that I mentioned at the beginning. As far as we can tell it's [Inaudible] but it sounds like, from the public comment we've received, that it has been accepted and we will continue to look for that. Again, this is by one of the same authors that previously did [Inaudible] I probably put it in the report. There are two short-term placebo controlled trials of Transdermal [Inaudible] Morphine, but this drug is not available in the U.S. so we have excluded it. [Inaudible] drug is undergoing the FDA approval process so we went to the FDA website, but we'll just need to keep an eye on that. We don't have [Inaudible] Hydromorphone yet. There's only published an abstract at this point and [Inaudible] cancer patient. We'll be keeping our eye out for that. [Inaudible] and Oxycodone, of course, this drug is not yet approved. It's undergoing the approval process and so far all we have are abstracts for that.

So, next slide. So in summary, we still only have three head-to-head trials. None are good quality. We await [Inaudible] and hydromorphone. Currently the FDA approval is only at the 2nd line agent people already on moderate doses of opioids. Two of the new trials were drugs that we didn't have trials on before; Levorphanol and Methadone. Both of these use unusual designs and in addition to other problems with comparison; because they weren't directly compared to other opioids the design makes comparison even more difficult. [Inaudible] quality is generally poor. We do have those two large California Medicaid studies that suggest that constipation may be less with transdermal Fentanyl than with Oxycodone, but again concerns about significant base [Inaudible] differences between groups with virtually any demographic variable that you look at. There is no evidence that one long-acting opioid is superior to others or that long-acting opioids as a class are superior to short-acting. We can [Inaudible] the risk for Methadone but unable to really look at that in context with the other drugs, though there is certainly concern and [Inaudible] generally excluded from these trials as no one's done a good observational study looking at that risk.

I think that's it. Next slide. Yeah, that's it. So, I guess we have time for questions, if anybody has questions.

Daniel Lessler, M.D.: Thank you, Roger, for a good update. I was going to open it to committee members for questions on the update for Roger.

Roger Chow: Great.

Daniel Lessler, M.D.: It doesn't look like there are many questions. I think the essence of your comments, Roger, really would suggest that there isn't much in the way of meaningful new data out there from a clinical perspective at this point compared to the prior report.

Roger Chow: No, I don't think so. I think the...you know, I should probably comment a little bit more about the constipation issue with Fentanyl because it has been looked at in cancer patients and the findings of those two observational studies are consistent with what's been seen in cancer patients. So it could very well be a real finding. But, you know, because we're really focusing on the non cancer [Inaudible] population, this is all the data we have. So just to kind of maybe take that into consideration that this may be kind of an emerging data to really look at. And I think the other areas really with Methadone safety, I mean, really it's getting a lot of attention. And Oregon, specifically is getting a lot of attention and I think elsewhere in the country the question of safety of Methadone combined with kind of a continued lack of good study on Methadone, this continues to be an issue. We just wish there were better studies on some of these drugs. So I'll just leave it at that.

Daniel Lessler, M.D.: Thanks. Jeff?

Jeff Thompson, M.D.: [Inaudible] talk a little bit about this other DUR...this is Jeff Thompson, but we at Medicaid are also concerned with the safety and efficacy in this class. You may have been contacted. We just launched our product notification program where we're notifying...we've identified the top three [Inaudible] clients who need ten or more prescriptions of narcotics by multiple providers in any one month and are providing you, the providers, the information of who is making those prescriptions and whether they're getting those from emergency rooms. So we are very concerned about this and trying to work with providers to talk with each other because we do not have a good system to track these. And we'll continue to work in that fashion.

Roger Chow: I think one of the issues with Methadone, especially, is conversion. Then the question is almost...and I think there are two separate questions. One is whether Methadone is inherently more dangerous than other drugs, which I'm not sure we have data on that. The other question is whether it's more dangerous because providers are using it inappropriately because they're not converting it appropriately, which is more of, I think of, an education issue than that the drug itself is more dangerous. But it's really hard to sort those things out and I'm not sure if you can sort them out. But to me they seem to be kind of two separate issues. But if you can [Inaudible] providers are using the drugs appropriately, which is what we hope they are doing, you know, how safe are they...that's really the question we want to ask in an education component is maybe a separate thing. Yeah, it continues to be brought up, and like I said, it was, you know, front page in the Metro section in The Oregonian yesterday the Methadone death issue.

Daniel Lessler, M.D.: [Inaudible].

Carol Cordy, M.D.: I have a question, Jeff. Carol Cordy here. Are there any...do you have any data showing an increased use of Methadone preferred on the Preferred Drug List?

Jeff Thompson, M.D.: Well, I think you basically...back prior to November of '03 there was about 70% utilization of brand drugs. Once prior authorization of the Preferred Drug List came into effect that has gone down to 30%. So like I don't have the actual numbers, but the increase of preferred drugs, Methadone to long-acting morphine [Inaudible] has increased [Inaudible]. They are the preferred drugs. They are now 70% of the market share. They used to be 30% of the market share.

Carol Cordy, M.D.: And does Washington have numbers like Oregon?

Jeff Thompson, M.D.: We...there are published data, I mean, from DOH looking at a number of excess deaths relating at both illicit and non illicit drugs; Morphine, Methadone...I'm not clear about Fentanyl and some of the other ones, but I know the Department of Health a number of the officers are concerned about overdosing [Inaudible] drugs. And we are working with them and that is why at least starting with the top 300 working with positions. We're also included in that, those top 300 clients are being referred to the PRO program where they would be restricted to one physician, one hospital and one pharmacy. And then we're also working with GOTHA to refer those top 320 clients over for basically [Inaudible] consideration for money for drug treatment. So we're doing a lot. I think it's a very good balance of looking at the balance equation for looking at access to look at quality and we're tending to cost issues [Inaudible]. In my mind I think its working. I think there's a huge amount of education that needs to occur in data sharing at the provider level to take care of some of these other issues that are occurring with [Inaudible].

Carol Cordy, M.D.: And how was that number...ten seems awfully high.

Jeff Thompson, M.D.: There's some published data on where you do the cut point. Obviously the sensitivities best fit the issue. The further down you go...five or more you start getting into is it medically necessary, not medically necessary. There's published data on this that it was...we looked at the numbers and said this is something we could do in pilot. This is something that seems to be [Inaudible] abuse and misuse. After three months we'll come back to you and basically tell you what the results are. Actually if it's greater than ten prescriptions for schedule two, schedule three in any one month of last year or seven or more prescriptions in any six-month period or the two certain cut points. Not really good data to say, you know, where it is 100%. And I might include, though, this does not include oncology clients and this does not include hospice care. So this is non oncology, non hospice care.

Daniel Lessler, M.D.: Are there any other questions for Robert? Patty?

Patti Varley, ARNP: This is Patti Varley. A question. When we made this motion previously, which led to the changes from brand to more generic use, and I know there was at least some issue with conversion, do we have any data about the implementation of what we did in regard to safety data? In regard to death or injury from the motion we made before?

Roger Chow: Related to deaths we have not combined that database. It's something that we can look at [Inaudible]. I have not heard [Inaudible] from the providers around...I mean, that was a concern but it's really calmed down.

Patti Varley, ARNP: I know with Methadone we don't really encourage it as a preferred drug it's just drug if they feel comfortable using it or if they're familiar with it. I think we more...you know, we ask them to try long-acting morphine generic, but we don't really ask them to try Methadone unless it's their choice. We try to keep that to their discretion because of those issues that they don't know how to use it. We don't want them to try.

Roger Chow: And we also add it on the second round as one of the preferred drugs after we [Inaudible] preferred drugs, Methadone, long-acting Morphine or [Inaudible] currently the preferred agents. It is a concern. It's very difficult to actually tie cause and effect. We are working with coordinates. This is a big push for us so the more we get educated and we educate the provider community we're doing due diligent, probably not enough.

Man: What is the most used drug in that preferred category?

Nicole: It's the morphine. Yeah. I don't know...I wish I knew the numbers, but I think most of the increase has been in the morphine. But I can't tell you the exact number [Inaudible]. Like the generic [Inaudible]. I have a question for Dr. Chow

Roger Chow: Yes.

Nicole: This is Nicole with Washington Medicaid. I was just trying to remember if you...I don't know if you've seen this, it was Cathy Ketchum down at Oregon. I remember her doing a presentation on the Methadone test in Oregon State where they took out data. I don't know...have you seen this and am I remembering it correct? [Inaudible]...

Roger Chow: Yeah [Inaudible]...

Nicole: And there was no increase in Medicaid clients specifically?

Roger Chow: I kind of vaguely remember it. I think it was...I think what they did was they controlled for prescription use, but they kind of found the same thing that the state found overall, that numbers of deaths did go up but it was because...or it seemed related to the fact that you were doubling or tripling the number of people getting Methadone. But I believe the results were very similar from the results that the State reported as a whole.

Nicole: Thank you.

Daniel Lessler, M.D.: Where I see the biggest issue is the lack of connectivity between both prescribing versus what you prescribing. I mean, it's really very amazing for these [Inaudible] clients that we have identified with ten or more prescriptions that touch about 3,000 physicians.

Daniel Lessler, M.D.: [Inaudible].

Man: Questions for Robert? We do have one stakeholder signed up to speak here. Then...I just wonder if there's any effort that's being made to look at our Methadone overdose rates and whether they've changed at all. Sounds like in our state Methadone's just not used much. Probably...it's not going to be like Oregon where there's a real increase in usage in Methadone whereas we haven't. So it may be just a moot point as whether we should look at that. But is there an effort made to look at those deaths and the numbers and whether there's been any change?

Roger Chow: We'll report back to you in September if I can connect and work with Maxine [Inaudible] of Department of Health. We'll look at that. So far we haven't gotten the feedback, but we are working with the Department of Health. But I'll report back to you.

Daniel Lessler, M.D.: We do have one person signed up, Dr. Nancy Lewis.

Nancy Lewis: My name is Nancy Lewis. I am a pharmacist. I have experience...clinical experience in clinical care, oncology and pain management. I am currently employed as a medical liaison with Purdue Pharma, and today I am going to briefly discuss one of our products, Oxycontin, which is the [Inaudible] release. The need for today's discussion really is based upon current surveys indicating that as many as 50 million AmErikans are at least partially or completely disabled by persistent pain. [Inaudible] the cost of uncontrolled pain to [Inaudible] at a cost of \$100 billion each year in health care utilization expenses, lost productivity, compensation and litigation. In a statement to the US Food and Drug Administration the Anesthetic and Life Support Drug Advisory Committee Dr. Richard Payne, who has been the president of the AmErikan [Inaudible] Society, noted that for many patients one drug does not fit all. Studies indicate that 80% of patients they require one switch of opiate medications and 20% of patients require three or more switches of medications to manage their pain in the most optimal manner. Even though opiates derive from the same general chemical family, there are important chemical differences in the ways in which patients respond to specific drugs. Therefore, it's essential to have many opioid medications and formulations available for clinicians to provide [Inaudible] clinical possibility that allow optimization of therapy and individualization of treatment of patients. In addition, the treating clinician needs to take differences in potency, side effect profiles, metabolites, [Inaudible] kinetic profiles and delivery systems into account based on the individual patient's situation. With this in mind, I'll now briefly discuss Oxycontin.

Oxycontin tablets are indicated for managing moderate to severe pain with continuous, around-the-clock analgesic [Inaudible] for an extended period of time. It is not indicated for p.r.n. use. The safety and efficacy of Oxycontin has been studied in moderate to severe pain due to various etiologies which include cancer, osteoarthritis, diabetic neuropathy and post-herpetic neuralgia. It provides analgesic within 1 hour in most patients and prolonged pain control [Inaudible] 12-hour dosing. So the most common side effects seen with Oxycontin include constipation, nausea, somnolence, dizziness, vomiting, [Inaudible], headache, dry mouth, sweating, and weakness. Severe adverse reactions are those observed with other opioid analgesics including respiratory depression, hypertension and shock. Oxycontin tablets are to be swallowed whole and are not to be broken, chewed or crushed. Purdue Pharma has designed a

risk management program with the goals of facilitating proper patient selection and use of Purdue's schedule II opioid analgesic, reducing abuse, minimizing diversions and avoiding pediatric exposure. The programs also provide extensive medical education, sales point training, detailed prescribing application, medical surveillance and appropriate interventions when needed. According to the [Inaudible] Society, principles of analgesic use and the treatment of acute and cancer pain, some patients appear to tolerate analgesic doses of one opioid better than another and it's often useful to try a different opioid if the first one is poorly tolerated.

In conclusion, I would like to urge this committee to facilitate safe and effective pain care for Washington citizens who suffer from persistent pain by choosing to have a wide array of long-acting opioid options available to the Medicaid population. Thank you.

Daniel Lessler, M.D.: Thank you. Yes, [Inaudible].

Man: [Inaudible].

Daniel Lessler, M.D.: That's okay.

Bill Strike: For the record my name is Bill Strike. I represent Johnson & Johnson. I'm not a scientific person but I do feel compelled to respond. Nicole, we'll follow up. One of the differences between Washington and Oregon is in Oregon you can't prior authorize a drug for [Inaudible] Medicaid. You can't subject it to any restrictions. Where they saw the increase in deaths, as I understand it, with respect to Methadone, was in the managed care organizations that preferred Methadone. So...and I would just call your attention to that fact. The other thing, and this would be a comment for Dr. Chow, we note in your [Inaudible] data, a 641% increase in Fentanyl matches, but the base of that was extraordinarily low and it doesn't discern between long and short acting and we will scrub that data and make Dr. Thompson aware of this and he can supply you that information. Thank you.

Daniel Lessler, M.D.: Thanks.

Roger Chow: Yeah, thanks for that comment. Yeah, that is correct that the number of Fentanyl deaths...Fentanyl mentions, excuse me, were very low at the initial start of the [Inaudible] and that's one of the reasons why that number looks so big. Of course in the [Inaudible] getting all the nuances into it. But thanks for clarifying that.

Daniel Lessler, M.D.: Are there...is there any other stakeholder input at this point? All right. I would call the committee's attention to...we have deliberated on long-acting opioids previously and on page 11, under the tab Drug Review History, page 11 has our previous recommendation and that is from a year ago June. Yeah?

Woman: I've also pulled the official motion out of the previous minutes and that's what's up on the screen at this time.

Daniel Lessler, M.D.: Thanks a lot. That's helpful. So people can take a moment to review what we had previously and the motion. You know, Jason, I'll read that for you. I just realized...are you there?

Jason Iltz, PharmD: Yes, I am.

Daniel Lessler, M.D.: Okay. So the previous motion was...this was in June of 2004. After considering the evidence available on safety, efficacy and use in special populations, I move that long-acting opioids are safe and effective when used appropriately and have similar adverse effects. There should be more than one preferred drug in the long-acting opioid class. So that was adopted on June 16, 2004. So, with that, I'm wondering if there are any other thoughts from the committee at this point in terms of...especially relevant to anything new that people might have heard or want to comment on relative to our previous motion. [Inaudible], anything just makes...try not to forget you up there.

Jason Iltz, PharmD: No, I think the previous recommendation sounds like it really holds true today as well.

Daniel Lessler, M.D.: Would you like to make a motion?

Jason Iltz, PharmD: Am I supposed to remember what you just read?

Daniel Lessler, M.D.: Oh, you can just said, I think as we did previously, that...something to the effect that we recommend...how did we put it last time? I guess it's...

Jason Iltz, PharmD: I'd like to move that our previous recommendation move forward to today.

Woman: After reviewing...

Jason Iltz, PharmD: The update.

Daniel Lessler, M.D.: So after reviewing the updated information we recommend that the...our original motion stands. So is there...

Man: I second.

Daniel Lessler, M.D.: There's a second. Great. Any other discussion? [Inaudible]?

Man: Doesn't really affect us, but I guess maybe somebody can remind me since the studies do show the long-acting opioids are no better than the short-acting opioids, why are we doing this? Why are we separating the long-acting opioids?

Man: The drug abuse are basically defined [Inaudible] OHS [Inaudible] basically said we need to look at this drug class. In that drug class they chose that specific narrow definition long-acting for non oncological [Inaudible].

Man: So I'm just...in other cases we don't separate long-acting and short-acting [Inaudible].

Man: And it basically, I believe, it was the determination of the multi-state cooperative working with OSHU to define the scope of the OHSU reviews [Inaudible] were the most problematic, were the most [Inaudible] interest and [Inaudible].

Daniel Lessler, M.D.: Any other comment or discussion?

Roger Chow: Just going to try to add something to make it real clear and then have you read it as a [Inaudible].

Daniel Lessler, M.D.: All right. Roger, I think...we appreciate your joining us. I think you can...we can dismiss you here. So thanks a lot.

Roger Chow: Great. Thank you.

Daniel Lessler, M.D.: Take care.

Roger Chow: All right. Bye-bye.

Jenny Mark: Hi, this is Jenny Mark of Labor & Industry. I wanted to bring up a point. With this review there's a new drug, [Inaudible] that has very specific indication and some risk management program to go along with that. And so I don't know whether or not that should be addressed in as part of the recommendation.

Daniel Lessler, M.D.: Which?

Jenny Mark: That's the Hydromorphone sustained release.

Daniel Lessler, M.D.: Sustained release. They did not...that hasn't been reviewed. I think that was Roger's point.

Jenny Mark: Okay. So it hasn't...it's not going to be included in this. [Inaudible] abstract [Inaudible].

Daniel Lessler, M.D.: Right. So...are we there? So let's...after reviewing the updated information on long-acting opioids, the previous recommendation to the class...okay. After reviewing the updated information on long-acting opioids, our previous June 16, 2004, recommendation remains in effect. I'll say that the motion has been seconded. All those in favor, Aye.

Group: Aye.

Daniel Lessler, M.D.: Opposing [Inaudible]. Okay. So the motion passes. Jeff, in terms of [Inaudible].

Jeff: [Inaudible] 12:45.

Daniel Lessler, M.D.: 12:45. Okay. Thank you.

[break]

Daniel Lessler, M.D.: Hi, Kim, it's Dan Lessler.

Kim Peterson: Hi, Dan.

Daniel Lessler, M.D.: And I think we've got a quorum back from lunch here, so we're going to reconvene and continue with our agenda.

Kim Peterson: Okay.

Daniel Lessler, M.D.: Kim Peterson on the phone and our next topic is an update on calcium channel blockers. So, at this point what we have in front of us is your power points projected and the title slide is up and so you could just take it away from there.

Kim Peterson: Okay. I'm Kim Peterson and I'm the Project Coordinator for the [Inaudible] Review Project, the Oregon [Inaudible] and I'm going to be presenting the new evidence from the second update of federal class review of calcium channel blockers. And with regards to the slides, I'm not going to spend time going through all of them in detail, and I know that your group has reviewed them on previous occasions. Instead I'll focus only on the slides that reflect new evidence and comments regarding how the new findings impact our previous conclusion. So for slides two and three, those reflect our methods, you've seen those before and there were no changes to our methods for the second update. Slides 4-7 reflect our key questions and eligibility criteria. You've seen those before and those specify our eligible population intervention and study designs, and the only change here is that we expanded the study design criteria for safety data to include observational studies. Slides 8-11 provide an accounting of the number of studies we've included stratified by population and design. And update number 2 we added 23 studies, and these include 5 active control trials in patients with hypertension, one placebo control trial in patients with [Inaudible] that reported long-term health outcome, and 17 observational studies including 9 that reported the risk of cancer. Three that reported the risk of cardiovascular [Inaudible] mortality and 5 that reported other adverse events. The 5 [Inaudible] controlled studies we added included value, which is the study of Amlodipine vs. Valsartan in patients with high cardiovascular risk. And this is a study for which we previously only had the [Inaudible] publication and now we have the results. The second active controlled study is IDNT. This is a study of Amlodipine vs. [Inaudible] in patients' co-morbid for Type II diabetes and protein urea. The third active controlled study is the JMIBC, and this is a study of Nisoldipine [Inaudible] vs. various Ace inhibitors and Japanese patients with coronary artery disease. The fourth active controlled study was conducted by Peterson et. al., and this is the study of Isradipine vs. Spiropril in patients with chronic renal disease. And the final active controlled study was conducted by Fletcher et. al., and this is a study of Isradipine [Inaudible] vs. Atenolol or (inaudible). And this study only reported quality of life outcome.

So this, the evidence from these five new active controlled studies has been combined with the pre-existing active controlled evidence and that evidence is all summarized on slides 12-17.

Daniel Lessler, M.D.: Kim, we don't have numbers on the slides.

Kim Peterson: Okay.

Daniel Lessler, M.D.: What would be the title on that slide?

Kim Peterson: The title on slide 12, Comparative Efficacy of Calcium Channel Blockers for hypertension. And that slide outlines the number of [Inaudible] studies. The second slide summarizes the overall [Inaudible] for quality of life efficacy. And then the remainder of the slides, 14-17, point out the heterogeneity issues and then the evidence for all the [Inaudible] that reflects the results for all [Inaudible] mortality outcome for the calcium channel blocker vs. ace inhibitor or angiotensin [Inaudible] comparison, and then [Inaudible] reflecting outcomes of all commonality for all calcium channel blocker versus diuretic or beta blocker comparison. And the evidence from the new site from the new studies has been integrated into these sites. And I wanted to just point out that...or just highlight in words the evidence from the new studies and how they fit into the previous evidence.

So, with regard to the new evidence, there were no differences between Amlodipine or Nisoldipine and the respective A2RA or Ace inhibitor comparators for rates of all cause mortality, cardiovascular disease mortality, fatal or non fatal stroke, or fatal or non fatal heart fatal in the value IDNT and JMIBC studies. However...

Daniel Lessler, M.D.: [Inaudible] again.

Kim Peterson: Sure, sure.

Daniel Lessler, M.D.: We're really having difficulty identifying where you are with the slides.

Kim Peterson: Okay. I'm not on the ...I'm not on any particular slide.

Daniel Lessler, M.D.: Okay.

Kim Peterson: I just pulled out what the evidence from the new studies are.

Daniel Lessler, M.D.: Okay.

Kim Peterson: Mostly from the report. And its evidence that is summarized in slides 13-17, but prior to these slides I realize they're hard to follow in the sense of just looking at what the new evidence is. So for this part these slides aren't all that helpful, I realize.

Daniel Lessler, M.D.: Okay.

Kim Peterson: Should I continue?

Daniel Lessler, M.D.: I think we're okay now.

Kim Peterson: Okay. So I had summarized the evidence that there were no differences between Amlodipine or Nisoldipine in mortality and morbidity outcome than the value IDNT or JMICB studies. You can find...you can see this...on the slide that's entitled All Cause Mortality relative risk 95% confidence interval, for...you can see these results, I guess, in terms of trying to figure out how this fits into the slide presentation on the slide 15 that's entitled All Cause Mortality for Calcium Channel Blocker vs. Ace Inhibitor or HURA. You can see the IDNT and value studies there.

Daniel Lessler, M.D.: [Inaudible] no, go to the next slide.

Kim Peterson: Do you have that slide.

Daniel Lessler, M.D.: For some reason, it didn't come out. It might have been a problem with my copying or something. I don't know. But we have hard copies.

Kim Peterson: Oh, okay.

Daniel Lessler, M.D.: Let me, Kim, just make sure everybody's...it's, again, looking at the slide that sort of plots the relative risks against one and shows the confidence intervals around those and...

Kim Peterson: Mm hm.

Daniel Lessler, M.D.: Okay. So, just as long as...the committee in the right place there? Okay.

Kim Peterson: It's just to show...it's the graphical display of [Inaudible] that there were no differences between either Nisoldipine [Inaudible] or the ace inhibitor comparator or in the IDNT study no difference between Amlodipine and [Inaudible] and in the value study no difference between Amlodipine and Valsartan. And so the way that we summarize this to display it graphically in a [Inaudible] plots.

Daniel Lessler, M.D.: Kim, when you say no difference you're talking about cardiovascular mortality?

Kim Peterson: All cause mortality.

Daniel Lessler, M.D.: All cause mortality. Okay.

Kim Peterson: Mm hm. But, in fact, there are also no differences. This is not reflected in the file, but in fact, yes, there were also no differences in cardiovascular disease mortality. Or fatal or non fatal stroke, fatal or non fatal heart failure. So the only outcome in which there was a difference between a calcium channel blocker and an ACE inhibitor was in the IDNT study and the value studies. And in those studies Amlodipine did reduce the risk of fatal or non fatal myocardial infarction when compared to the respected HURA comparators. And then keep in mind the other studies of hypertensive a patient that were co-morbid with either coronary artery disease or best of value study or diabetic neuropathy...or [Inaudible] sorry, that's the IDNT study. But at the same time Amlodipine was associated with a significant greater risk of heart failure than [Inaudible] in the IDNT study.

Okay. Now the Peterson et. al. study, let's see if I have a slide for this. I don't think so specifically. The focus of the slides was on the outcomes in all cause mortalities. So this additional information I'm presenting is in the report but it's not reflected in the slides. It's just to say that the other two...it's just to summarize the results of the remaining two new active controlled studies and that is the Peterson et. al. study only reported renal outcome. And in this study its Nicardipine and Spirapril were associated with similar rates of end stage renal disease. And then in the Fletcher et. al. study, there were...the results were mixed across the different quality of life outcome for Nifedipine retard, [Inaudible] or Atenolol.

So, in summary, the bottom line is that the addition of these trials did not improve our ability to clearly differentiate one calcium channel blocker from another for efficacy as these new trials were similarly heterogeneous with regard to population, variations in comparator drugs and the usage of additional anti-hypertensive medications, and we also have the same concerns about these trials regarding potentially insufficient power.

Okay. So I'm going to move onto the next slide, 18, which entitled Comparative Efficacy of Calcium Channel Blockers for Chronic Stable Angina. And this is...so this is the one new placebo controlled trial of Nifedipine, gastrointestinal transport system. The results of which are summarized on this slide and also on page 22 of our report. And this is a trial of 7,665 patients that were followed for 4.9 years. And Nifedipine DITS did not significantly reduce the number of deaths due to any cause or rates of mild cardio infarction, refractory angina, stroke, percutaneous coronary intervention or peripheral revascularization. Nifedipine did really reduce rates of some secondary outcomes, however, and those included overt heart failure, coronary angiography and coronary bypass surgery. So in summary, results from this placebo controlled trial do not change our previous conclusion that for symptoms, consistent evidence from 13 head-to-head trials of Amlodipine, Diltiazem, Nisoldipine, Nicardipine and Nifedipine does not show a difference between these calcium channel blockers. Now with regard to slides 18-32, I realize you don't have the numbers; I'm not going to go through those at all because they summarize previous evidence and we haven't added any new evidence to these. So the next slide that I'll be looking at is slide 34 and that is entitled Long-term Safety and Cancer. So it's in the observational study would ensure that we found the remainder of the new evidence for update No. 2. Have you found that slide?

Daniel Lessler, M.D.: Yep.

Kim Peterson: Yep?

Daniel Lessler, M.D.: Yeah.

Kim Peterson: Okay. Okay. So slide 34 summarizes results from 6 cohort and 1 case control, 6 cohort studies and 1 case control study and these were all fair quality studies that recorded total incidents of cancer and cancer related mortality for Amlodipine, Diltiazem, Nifedipine and Verapamil compared to patients that were not taking calcium channel blockers. Unfortunately, these publications did not specify which formulations of calcium channel blockers were used not being either immediately released or extended release formulations. It's really difficult to make any assumptions about whether it was only the immediate release formulations that were used because there was overlap in terms of when extended formulations became available in the United States and when the data for these studies were collected as well as the fact that some of these studies were conducted outside of the United States. And so it's safe to say that the publications themselves just did not specify if there were any extended release formulations being considered here.

So in summary, with regard to total cancer incident rates, there was a suggestion that Verapamil and Nifedipine may be associated with significant increases in rates but results were mixed across the studies. There was no suggestion that Diltiazem or Amlodipine have been associated with increased risks in total cancer incident rates. With regard to cancer related mortality, there was no suggestion that Verapamil and Nifedipine or Diltiazem have been associated with increased rate. So, again, the only finding here is that there is a possibility that Verapamil and Nifedipine were associated significant increase rates in total cancer instance rate. But it was unclear...it could be assumed, perhaps that it was immediate release formulations only, but that was not specified in these publications.

Okay. Next slide entitled Long-term Safety in Breast Cancer. This slide presents results from two case control studies. One is rated good quality and the other was rated fair quality that are specific to breast cancer incidents. The immediate release [Inaudible] Diltiazem and Verapamil were not associated with an increased risk of breast cancer in the fair quality study of UK database, not being the general practice research database that was published in 2000. But were associated with increased risk of breast cancer in a good quality study conducted later in 2003 where data were derived via patient interviews. So you can see that the findings were mixed in terms of the association of immediately release [Inaudible] and increase in breast cancer incident.

With regard to the Dihydropyridine, there was no immediately release or sustained release forms that were associated with any increased risk in breast cancer across these two studies.

So, our overall conclusions about cancer, based on these studies summarized in the two slides that I just reviewed, are reflected in table 11 of our report on page 43 and indicate that these 9 studies really don't provide convincing evidence of an increased risk of total cancer, cancer mortality or breast cancer with the individual calcium channel blockers. Although, again, there were some findings that there was an increased risk for any cancer for Verapamil and

Nifedipine. And that one did find an increase in risk of breast cancer for the immediate release non-Dihydropyridines only.

Okay. Next slide, 36, entitled Long-term Safety summarizes all cause mortality from 3 good quality cohort studies. And so the first of these was a study of 51,921 post MI patients. A Hollis 1991 study. And also something to keep in mind, across these studies in terms of the general likeability of these findings are that these studies included patients that were greater than or equal to 65 years of age across all three of these studies. And in the first study, Hollis 1999, Bepridil was associated with an increased risk of all cause mortality when compared to patients that were not using calcium channel blockers, and this increased risk was not found for Amlodipine, Nifedipine, Diltiazem or Verapamil. In the second study, Maxwell 2000, this is a smaller study that involved 837 patients, and this was a broader patient population that was not restricted only to patients post myocardial infarction but was open to any patient that was using anti-hypertensive. In this study there was increased risk in all cause mortality associated with extended release Nifedipine but not with the immediate release form. And also there was increased risk associated with dosages that were above 40 mg/day of Nifedipine and also increased risk in all cause mortality associated with briefer durations of use. So durations of use that were less than or equal to 6 months. But the same pattern of increase in all cause mortality associated with extended release Nifedipine was not found for Diltiazem or Verapamil.

And in the final study, Gilman 1999, this again was a patient population of only patients that were post myocardial infarction and a sample of 833 patients. And in this study both Nifedipine and Nicardipine...immediate release formulations of both Nifedipine and Nicardipine were associated with increased risk of all cause mortality when compared to extended release formulations of these drugs. But, again, the difference was not found with Diltiazem or Verapamil.

So, our conclusions based on the evidence that I just summarized from this slide, is that the evidence provides a mixed picture with some indication that the long-acting formulations of Nifedipine result in lower risk when compared directly to the immediate release formulation, but when compared to beta blockers, the risk is higher with the long-acting form. And limited evidence suggests the higher risk of mortality with Bepridil compared to no calcium channel blocker while no increased risk with [Inaudible] with Amlodipine.

Okay. And the final slide that I'm going to summarize is slide 37, and it's entitled Adverse Events of Calcium Channel Blockers in Observational Studies. And this slide presents results from a few additional observational studies that presented tolerability rates. And in the first study this was a prescription even monitoring study conducted in the UK in which Isradipine was associated with the highest rates of flushing, headache and dizziness when compared to Diltiazem, Nicardipine and Amlodipine. And then Amlodipine was associated with the highest rate of peripheral edema when compared with Diltiazem, Isradipine, and Nicardipine. And a question had come up in another committee as to again whether this was...these were immediate release or sustained release formulations, especially with regard to Isradipine. And, again, this was not specified in the publication. A person could make an assumption that this was an immediate release formulation because the time during which the data was collected from

these individuals preceded when the extended release formulations were marketed, but it was not specified in the publication.

And finally, in a smaller study of adverse events during hospitalization, there were...the highest rates of severe adverse events were associated with Diltiazem followed in order by Verapamil, Amlodipine, Nifedipine and Nicardipine. And severe hypotension was reported most often with Amlodipine and bradycardia with Verapamil. And overall conclusions from adding these observational studies and tolerability outcomes to our previous randomized control trial evidence really don't...again, don't add to the fact that previously we could not clearly differentiate the safety of any one calcium channel blocker from another in any population.

And so just the final slide, 38-42, we didn't make any changes to. There was no evidence added to randomized control trial to [Inaudible] adverse events and randomized control trials or any findings specific to any subgroups, so I'm not going to comment on those slides. And this concludes my comments, so I'm open to questions at this point.

Daniel Lessler, M.D.: Thank you. And so we'll open up to committee members if there are questions, points of...

Kim Peterson: 'Kay.

Daniel Lessler, M.D.: clarification here.

T. Vyn Reese, M.D.: This is Dr. Reese. I'm interested in the cancer rates and risks. It sounds like from your summary that, even though some trials there may be a risk, your overall assessment is that there's not actually major differences in the calcium channel blockers, is that correct?

Kim Peterson: That was our conclusion. And we recognize that there were some differences, but overall the results were mixed. It's hard to make conclusions about them, about the differences.

T. Vyn Reese, M.D.: Along the same lines, I don't recall, can you just comment on the order of magnitude of the [Inaudible] ratios. Are they like 2 or less? Were they worse than [Inaudible] or were there any of them of greater magnitude?

Kim Peterson: Okay. That's a good question. I'm going to refer to the evidence tables to get that information for you. If you can give me a minute. So there are six studies with regard to the outcome of increased risk and incidence of cancer. There are four studies of Verapamil in two of which there were findings of increased risk associated with Verapamil versus two that did not find that same increased risk. And in the first of the studies that did the relative risk were 2.1. And then...

Man: If you can't find it that's okay. I didn't know whether you might have just known.

Kim Peterson: I don't know off the top of my head, but I could look up...what I'm doing is looking it up in Table 15. I'm looking at the results and trying to find that second study—the outcome measure there. As I'm sorting through this are there other questions that I might be able to answer quickly and I could come back to this one?

T. Vyn Reese, M.D.: Yeah, this is Dr. Reese. I had questions about systolic dysfunction. In our previous review we discussed how Amlodipine and Filodipine did not exacerbate heart failure in patients who were taking them whereas the other calcium channel blockers there was evidence that they may in fact exacerbate heart failure and here...I'm not sure what the statement is. It's comparison...Dyhydropyridine versus non Dyhydropyridine CCB's. Comparison not relevant in systolic dysfunction. I'm not sure what that statement meant. Does that mean that that is what we found in the previous review was not true or is that still the case that those particular Dyhydropyridines are safer in patients who have left ventricular dysfunction and the non Dyhydropyridines my understanding was that they were actually worse in that setting. They exacerbated heart failure and would be drugs to be avoided, as well as Nifedipine.

Kim Peterson: Okay, I'm sorry, which slide are you referring to or which statement?

T. Vyn Reese, M.D.: It's the fourth slide from the bottom – Dyhydropyridine versus non Dyhydropyridine CCB's. On ours they are not numbered so it's the fourth slide from the end.

Kim Peterson: Okay, so this is a slide from the previous review and hasn't been updated since that time. And so the question is...so your question...can you repeat your question?

T. Vyn Reese, M.D.: On the previous review we discussed how non-Dyhydropyridine calcium blockers were bad for patients who had left ventricular dysfunction. They clearly exacerbated left ventricular dysfunction whereas Amlodipine and Filodipine did not exacerbate left ventricular dysfunction and that was one of the differences between the drugs, the drug groups and also Nifedipine actually exacerbated left ventricular dysfunction. It had a negative effect, but then it said in this summary slide here the comparison is not relevant in select assumptions. I'm not sure what that means. Is that retracting that...are you saying you can't compare the two because they have such different effects?

Kim Peterson: Um, well, it's that there...a comparison can't be made in that population because there is only one poor quality study of a non-Dyhydropyridine. So there wasn't a basis for comparison within that population.

T. Vyn Reese, M.D.: So in other words they probably weren't studied because they had a deleterious effect maybe. Is that why? It's still confusing.

Kim Peterson: We were trying to make indirect comparison...we were able to make indirect comparisons across studies in patients...in studies that were published with patients of hypertension and angina. So able to make conclusions in those populations, but then not able to make conclusions in the systolic dysfunction population due to what the published evidence reflected and that is that all we had was...we had studies of Dyhydropyridine, but we only had

one poor quality study of a non Dihydropyridine so it impaired our ability to make those indirect comparisons so we just weren't able to reach conclusions in that population.

T. Vyn Reese, M.D.: I think I understand.

Kim Peterson: I can see that the not relevant could be improved.

T. Vyn Reese, M.D.: Right.

Man: Other questions for at this point? Kim, are you able to stay on the line about ten more minutes?

Kim Peterson: Sure.

Man: Actually, we were going to invite stakeholder input at this point and there were a few people who wanted to comment on calcium channel blockers. Again, we would ask that people limit their comments to three minutes.

Kim Peterson: Okay.

Man: Is Dr. Levy here? No. And then Dr. Roy Palmer?

Roy Palmer: Thank you. My name is Dr. Roy Palmer. I'm part of the medical team at Pfizer, but I'm based in Seattle. I'm talking about Amlodipine, Norvasc. Obviously the last time you [Inaudible] the calcium channel blocker class and I remember discussion, it was the weight of the clinical data which made you decide to put Norvasc on as a preferred agent and I would like to talk about two pieces of data which haven't been included in the argument report. One because it's too recent and that is the Ascot blood pressure trial. That's a comparison of Amlodipine and an ace inhibitor compared to a beta-blocker and a diuretic. There was a study conducted in 20,000 patients, primary prevention population with additional risk factors and conducted over five point four years. The study was stopped early this year because of the significant 15% benefit in mortality in favor of the Amlodipine and ace inhibitor arm as compared to the diuretic and beta blocker arm and this data was...at the AmErikan College of Cardiology they took the very unusual step of presenting this data still in it's slightly preliminary form because of the importance that they felt this data represented and what we know at this point, and until the complete paper is published, which is why the Oregon Report hasn't reviewed it, what we know at the moment is there is a significant 15% mortality benefit in favor of Amlodipine and the ace inhibitor.

So I think this adds to the weight of the evidence we have from the very largest clinical studies, when you consider Alhat had 40,000 patients; Value15,000 patients, and we showed safety and efficacy in cardio vascular outcomes equivalent to ace inhibitors, [Inaudible], diuretics. And I think none of the other agents in this class have this kind of data and if you look at many of the other studies, they are very small studies. Until you evaluate the agents in these large clinical studies there is a lot of uncertainties, a lot of unknowns.

Some other considerations for you is the (Inaudible) study. You talked about systolic heart failure and Amlodipine is the only drug to have shown, in a large clinical study safety in phase stage 3 and 4 heart failure patients. Another factor, Amlodipine has no drug interactions whatsoever, absolutely none, and there aren't many agents in this class or any other who can say that. It has an intrinsically long half-life and in addition 1 and 4 in factors that it is crushable meaning it can be used in feeding tubes and mixed in with food, which is especially useful some physicians find with pediatrics.

So in summary I would like you to again consider the vast body of evidence we have from Amlodipine, which we don't have for any other agents and if you would consider reinforcing your decision of last time and selecting Norvasc as preferred calcium channel blocker. Thank you.

Man: Thanks. I think that is...those are the only two people I had listed for comment on calcium channel blockers. Am I missing anybody? Okay. So maybe we can just turn to...again, I think I asked the committee to turn to our previous recommendation on calcium channel blockers and that's on page 8. It's sort of the fact side of...on the other side of the beta-blockers under the tab drug review history. And I'll just...to remind people what that recommendation was and that was made just a year ago. All generic forms of Verapamil and Diltiazem are to be the preferred non-Dihydropyridine and Nifedipine XR and Amlodipine are to be the preferred Dihydropyridines and all calcium channel blockers can be subject to therapeutic interchange within their respective subclasses. So that's where we were at just a year ago. With that I'll invite committee members to comment in light of what was presented whether people feel there is compelling evidence to change that at this point.

T. Vyn Reese, M.D.: Dr. Reese. I don't see that there is much new. I mean it's even more confusing having partial bits of data, but nothing much...except for maybe the Ascot study and some other newer ones that we haven't had a chance to look at yet. So I don't see there is much new and I wouldn't change what we've already done. That is sort of my gut just looking at it.

Man: Any other comments. Jason, are you there?

Jason Iltz, Pharm. D.: I'm here.

Man: So if there is no other comment I'm wondering if somebody wanted to make a motion along the lines of just keeping the same recommendation as we made a year ago. I can't remember quite the language we have been using around that.

Patti Varley, ARNP: This is Patti. I wonder if it is possible to look at what we did with the last statement and just replace it with the calcium channel blocker. It's the consistency in language.

Man: Kim, I think we're all set. We appreciate your time and your review. Thank you very much.

Kim Peterson: Oh you're welcome. Thank you, bye.

Man: Bye.

[Period of silence]

Man: So it would be after reviewing the updated information on calcium channel blockers. It is also a June 16, 2004 recommendation. I will just go ahead and make that motion. After reviewing the updated information calcium channel blockers our previous June 16, 2004 recommendation remains in effect, which is the above.

Patti Varley, ARNP: This is Patti Varley. I will second.

Man: Okay. Is there any further discussion? Okay. All those in favor, say “Aye”.

Group: Aye, Aye, Aye

Man: Opposed same sign. All right, the motion passes and we can move on to the next drug class. Jeff, so I see we actually have a slide presentation.

Jeff Thompson, M.D.: We have it if we want to use it.

Man: Let me ask just to get a sense of the committee. We do have a slide presentation or PowerPoint on drugs for over-active bladders. I think people probably had a chance as well to review the update and do people want to walk through the slides or do folks feel comfortable enough with...having the slides in hand just to engage some discussion and then stakeholder input. Does anybody feel strongly about presenting the slides as a collective group? On the screen or...?

Man: We can do them...

Man: All right, why don't we...Erika, can you pull that up? That would be great, thanks. And we can just walk through it together. If everybody wants to look at the handout on drug class review on drugs for over-active bladders. So I think the search strategy and data collection analysis piece is pretty much the standard approach. As far as inclusion criteria, included populations included with urge incontinence or irritable, overactive bladder. The medications that were included both immediate release and long acting or extending release were available were Oxybutynin, Tolterodine, Flavoxate, and Trosipium Chloride. The outcomes... the objective efficacy measures were changed in continence episodes for a 24-hour period and change in micturitions for a 24-hour period, as well as subjective patient assessments of symptoms. The key questions included comparative efficacy and comparative safety as noted. With respect to results there were 55 studies included. No study was rated good quality. Twenty-one head-to-head trials for comparative efficacy, five of which were poor, six were fair. Thirty-four non-drug therapy, other drug therapy or placebo controlled trials included for the efficacy portion and five observational studies were included to assess safety. With respect to comparative efficacy of Oxybutynin versus Tolterodine comparing immediate release to immediate release there were four trials of fair quality that were included and no differences based on objective or subjective efficacy measures and overall the [Inaudible] evidence was fair.

Next, for evidence on comparative efficacy of immediate release versus extended release first Oxybutynin immediate release versus Oxybutynin extended release there were no important differences in efficacy across three trials. Then Tolterodine immediate release versus extended release there was one trial. Overall no important differences in efficacy between extended and immediate release and median number of percent change in incontinence episodes and no difference in mean absolute change in incontinence episodes, micturitions or pad use.

With respect to comparing Oxybutynin to Tolterodine for immediate release versus extended release, Oxybutynin extended release versus Tolterodine immediate release, there was one trial and the Oxybutynin extended release was more effective in reducing the number of incontinence episodes per week and micturitions per week. With respect to Tolterodine extended release versus Oxybutynin immediate release the differences were not significant. The median percent change in incontinence episodes, mean change in voids per day and subjective assessments. Overall on those trials the grade of evidence was fair.

With respect to comparing Oxybutynin...continuing with the comparison of Oxybutynin and Tolterodine extended release versus extended release the offer trial with 790 trials noted no significant change, mean change in urge incontinence episodes per week, which was the primary outcome measure. Mean change in total incontinence episodes or mean change in micturitions per week and the percent continent in week twelve was significantly higher in the Oxybutynin extended release compared to the Tolterodine extended release. With respect to Oxybutynin transdermal versus Oxybutynin immediate release, one trial, only six-week study, 76 patients and there was really no significant difference with respect to the outcomes studied. With respect to the evidence of Oxybutynin versus Tolterodine here with the Oxybutynin transdermal versus extended release Tolterodine, again only one trial and it looks like across...what the outcomes they studied again there were no significant differences. Evidence of comparative efficacy between Oxybutynin versus Trospium, Oxybutynin IR versus Trospium IR one trial, longer duration averaged 54 weeks. No significant differences micturition frequency and incontinence episodes or urgency. Physicians rated Trospium as “cure” in 29% of cases. Oxybutynin immediate release in 17% of cases. Patients were reported as providing practically identically figures. Continuing with comparative efficacy act of controlled trials, urinary incontinence versus other drug therapy, six trials included versus the drug shown. The results of two trials of Oxybutynin consistent with head-to-head trial results, results from one of four Flavoxate studies indicate lower efficacy than found with Oxybutynin or Tolterodine in head-to-head trials.

Again, comparative efficacy non-drug therapy controlled trials – five studies of Oxybutynin immediate release, four reported results consistent with head-to-head trials. The other trial reported outcomes that were not used by head-to-head trials. And here’s evidence of comparative efficacy in placebo-controlled trials. Oxybutynin immediate release and Tolterodine immediate release generally showed great effects reduction in micturitions and incontinence episodes than the head-to-head trials. Tolterodine extended release consistent with head-to-head trials in change in micturition frequency and incontinence episodes. Oxybutynin transdermal one trial only 3.9 mg base, a significantly different placebo. Degree of change in the incontinence episodes per day greater than the head-to-head trials. Trospium one trial similar

mean change in number of micturitions per day as seen in head-to-head trials and Flavoxate one trial no significant difference in mean change in the number of micturitions per day.

With respect to comparative adverse events long-term evidence is limited. Dry mouth is the most commonly reported adverse event for both Oxybutynin and Tolterodine and the rates of this and other adverse events were similar for both drugs. Evidence of comparative adverse events in longer term studies the IR preparations, Oxybutynin IR versus Tolterodine IR one longer term comparative observational study...okay; we've got it up here so if people want to...

Woman: Is that the right study?

Man: So this is Oxybutynin IR versus Tolterodine IR one longer-term comparative observational study at six months duration included, um, while significantly a higher rate of an earlier withdrawal was found with the Oxybutynin. Rates were high for Tolterodine as well and 32% of Tolterodine versus 22% of Oxybutynin still on drug at six months and that was significant. Next.

Evidence again of comparative adverse events in longer-term studies. Trospium versus Oxybutynin IR trial with 54-week average follow up. Overall adverse events were a little over 64% and Trospium versus 76% and Oxybutynin dry mouth was 33% in Trospium and 50% in Oxybutynin. Constipation was 7% in Trospium and 4% in Oxybutynin. Visual disturbances 3% in Trospium and 6% in Oxybutynin. Overall dropout rate was higher in Trospium's group, but 10% withdrew due to adverse events on Oxybutynin and 6% on Trospium.

Evidence in comparative events, short term evidence, this is the immediate release to immediate release. Overall adverse event in dry mouth rate significantly higher for Oxybutynin IR compared to Tolterodine IR with the extended release versus the immediate release. Incidence of dry mouth was less on the extended release than on the immediate release. And that was statistically significant in three or four studies and with respect to the transdermal Oxybutynin versus the Tolterodine immediate release incidents of dry mouth was significantly lower with the transdermal preparation of Oxybutynin.

Evidence of comparative adverse events short term Oxybutynin transdermal versus Tolterodine extended release, dry mouth was lower with Oxybutynin, but it was not significant and there was an application site reaction to transdermal of 26% versus placebo patch in the Tolterodine group. Extended release versus extended release – dry mouth 29.7% in the Tolterodine extended release versus 22.3% in the Oxybutynin extended release and that was statistically significant and Trospium versus Oxybutynin no difference in dry mouth. Overall severe dry mouth Oxybutynin was at 23% versus 4% overall adverse events were comparable and overall the grade of evidence was fair. Next.

With respect to evidence of withdrawals due to adverse events four of eight trials of Tolterodine versus Oxybutynin found fewer withdrawals in the Tolterodine groups. One in six trials of extended release versus immediate release formulations found significant differences in withdrawal rates. Tolterodine extended release was less than Oxybutynin immediate release. One trial of extended release versus extended release found no difference in withdrawals. One

trial of Oxybutynin transdermal versus long acting Tolterodine found fewer withdrawals in the Tolterodine group and two trials of Trospium versus Oxybutynin IR found low withdrawal rates in the Trospium group.

With respect to sub groups Oxybutynin versus Tolterodine, Tolterodine IR versus Tolterodine extended release. Reanalysis of sub groups at 1,235. [Inaudible] mean change in incontinence episodes per week extended release was minus 11.8% versus minus 10.1% in the immediate release. Overall study extended release was...versus immediate release was not significant. No other head-to-head trials assessing the impact of race, age, gender, [Inaudible] or other drugs were found. There is insufficient evidence to indicate a difference between urinary incontinence drugs based on subpopulation characteristics.

Summary of evidence. Comparative efficacy – Oxybutynin versus Tolterodine head-to-head trials do not provide sufficient evidence of clinically significant differences between Oxybutynin and Tolterodine in IR, ER or transdermal formulations. Non-drug therapy and other drug therapy trials support the findings of the head-to-head trials. Placebo controlled trials report greater improvements in the outcomes than the head-to-head trials. Trospium versus Oxybutynin immediate release – there is limited comparative evidence. There is no difference in objective measures. Subjective measures favored Trospium and Flavoxate. No evidence on comparative efficacy.

Comparative safety of Oxybutynin versus Tolterodine – short-term studies indicate Oxybutynin causes more dry mouth and overall adverse events, but withdrawal rates are not significantly higher. Short-term studies indicate that immediate release formulations cause more dry mouth and overall adverse events, but withdrawal rates are not significantly higher. A short-term study indicates Oxybutynin transdermal has a higher adverse event and withdrawal rates than Tolterodine extended release. An observational study indicates a higher withdrawal rate by Oxybutynin by six months, but rates for both drugs are high.

Finally, Oxybutynin versus Trospium in terms of the summary of the evidence...longer term and short term trials one each indicate lower rate of dry mouth overall in one, only severe in the other and withdrawal due to adverse events with Trospium. Other adverse event rate similar, overall drop out rate is higher in Trospium group in the longer trial and that's a summary of the evidence. So with that I'm wondering if there are any additional comments that anybody from the committee wants to add, or impressions. Angelo?

Angelo Ballasiotes: Angelo Ballasiotes. Did I miss it with regards to mental disturbances on these drugs? Are there any comparisons? Maybe I missed it, but I'm looking for mental disturbances on these medications.

Man: I don't think there's published data.

T. Vyn Reese, M.D.: It's Dr. Reese. Well, there are cautions on use of all these drugs in geriatric populations because they can effect mental functioning and cause any [Inaudible] side effects and confusion, hallucinations, those sorts of things. So the question is, "Is there a significant difference between the drugs?" There's definite caution in Oxybutynin and it's

already been mentioned in several reviews of these drugs and whether Tolterodine...but if you look at the side effects of Tolterodine it's also...the same side effects are listed there whether there is a significant difference is unclear, but they are certainly drugs that you have to use with caution in the elderly because of that particular side effect profile.

Angelo Ballasiotes: That's my concern because most of these drugs...this class of drug is used in an elderly population.

Man: Any other comment? I don't think that the...I'm not aware...are you aware, Jack?

Jack: No, but in the further...some of the further studies of this we're going to be asking that in that Oxybutynin is listed on the DeBeers criteria not to given to older folks, but we think of all the drugs...if that's what you're looking for should be listed because it probably has no more effect than any of the other...any drugs. So we're going to be looking at that specifically.

Man: Okay, thanks. So I think we can take stakeholder input here.

Daniel Lessler: I'm Dan. There are two new drugs out that have been released since this report has been completed and there will be an update coming out in December including those two new drugs. I've actually advised the pharmaceutical manufacturers of those...or have released those two drugs that we won't be considering their comments today because there were not covered in this report. And both of those companies I believe they have already submitted their dossiers to Oregon, the Center for Evidence Based Policy to be included in that review.

Man: Thanks. So first on my list here is Dr. Kirk Harris.

Kirk Harris: Thank you for allowing me to speak with you today. My name is Kirk Harris. I'm a solo family physician and I started my Gray's Harbor rural family practice in 1991 and I have extensive experience in treating overactive bladder. I'm voicing my support of Detrol LA being the first choice on the Washington State PDL for the treatment of overactive bladder. The current status of generic Oxybutynin being the preferred drug is a concern to me because of its safety and side effect profile, as well as potential medical liability and its associated costs. As you've heard from the OSHU 55 study analysis all of these medications are efficacious; however, generic Oxybutynin has side effects significant such that it may be intolerable. These side effects are listed in the Merck Manual as weakness, sedation and anti-cholinergic side effects and that if possible should not be used in the elderly. This drowsiness that Oxybutynin causes may contribute to falls and injuries, increased hip fractures, nursing home admissions, it may impair driving ability and cause increased motor vehicle accidents, increase in mortality and morbidity.

Facts and comparisons 2003 states, "generic Oxybutynin should be only used with caution in the elderly, or in anybody driving or performing tasks which may require alertness, coordination or physical dexterity." DeBeers criteria also from 2003 indicate that it is a potentially inappropriate medication for the use in the elderly. A study by (inaudible) in 2001 indicates that generic Oxybutynin causes significant CNS depression as measured by quantitative EEG measurements. It's the only one of the five that significantly crosses the blood brain

barrier. We've come a long way since the 1970's when Oxybutynin was introduced to the market and now we have Tolterodine extended release or Detrol LA with a significantly improved side effect profile it has tolerability therefore dosing compliance and clinical effectiveness with improved patient quality of life. It is a more bladder specific medicine. I have found Detrol LA to be one of the most effective medicines and well tolerated for the treatment of overactive bladder. Also considering that it is the most cost-effective, the LA form is cheaper than the immediate release form. We need to take all aspects of cost into consideration not only pharmaco-therapy, but overall patient care and medical needs. So I urge the committee to make Detrol LA first choice on the Washington State PDL providing superior safety and tolerability for our Medicaid and uniform medical plan patients.

Man: I'm wondering if the Merck Manual has anything in there about Detrol. In the Merck Manual if you could read us that.

Kirk Harris: The list of medications referred to are Carisoprodol, Chlorzoxazone, Cyclobenzaprine, Metaxalone, Methocarbamol and Oxybutynin.

Man: So it doesn't have anything in there about Detrol?

Kirk Harris: No, sir.

Man: You're reading from [Inaudible] indicated in the elderly not probably the side effects profiled updated?

Kirk Harris: Yes.

Man: Thanks. Okay, thank you.

Jim Gasparich: Hi, I'm Jim Gasparich. I'd like to thank the panel for allowing me to speak here today. I did my residency training in Urology at the University of Washington and I'm presently Chief of Urology at Swedish and Providence Hospital in Seattle. I've been in practice now for 20 years in a couple of weeks. I'd like to give a more kind of clinically oriented perspective as someone who is actually treating patients and seeing the problems on a day-to-day basis. I know there are pharmacists on this panel who could know more about what I do with an M1 and M2 receptors and anti-cholinergic properties, but I don't want to debate into that. I just want to talk about kind of the life in the trenches so to speak and what it's like treating the patients.

I strongly feel that another option for treating overactive bladder is necessary in the formulary. I think, you know, this is a big problem and with a lot of both medical and kind of psychosocial side effects and if there is good treatment available I think, you know, the patients deserve it. Over my career I've seen a lot of changes in this treatment because initially, really the only medication was generic Oxybutynin and the patients would come back to the office and say, "Well, yes, their urge incontinence was better and they were doing better," but they would look at me sheepishly and they would say, "Well, they had to stop the medication because their mouth was so dry or they had terrible constipation or they have visual disturbances," and it was

really difficult because it was a competing interest between not being incontinent, but having a lot of side effects and when the newer agents came into use here not that long ago it [Inaudible] changed the whole clinical practice because now the risk...benefit ratio kind of swung more towards where the patients could tolerate these medications until they could improve their incontinence and their urgency and their frequency. I mean I think there are several trials that show the discontinuation rate with generic Oxybutynin are around 80 to 85% and that pretty well fits with my clinical experience and I was happy to see those clinical reports because it made me feel that I'm not a bad doctor who is not presenting this properly, it's just that's life. I mean I tried to get around and I still try to get around to my patients who from say a cough perspective need to take the absolute least expensive medication. If I used Oxybutynin I have cut them in half. So they are taking 2-1/2 mg a day. If I have them take 3 or 4 times a day and space it out and see if somehow they can get around the significant side effect. I think that brings in compliance issues because it's harder to take a drug 3 or 4 times a day than it is say once a day with the extended release formulation. I also feel that with these newer agents such as, you know, the long-acting Tolterodine the primary care doctors who are smart people can take care of this problem themselves because they've got a safer, easier drug to use. The patients will take it and I think there will be fewer referral [Inaudible] urologists because I don't want to see kind of uncomplicated urinary incontinence. I want to see the complicated cases. I think the more cost to the state in urology referrals if these patients get kind of ferreted to me because they can't tolerate the first find treatment that their own doctors have given them.

Out of all the drugs available, and there has been several new ones that have been eluded to, I think that the long-lasting Tolterodine or Detrol LA is the one that most of us are comfortable with, that have experience with it. I think if you were to poll the urologists in the State of Washington I think...I have no doubt it would probably be the agent of choice and I think if we are going to have another option that should be it and I strongly urge – no pun intended that the panel consider approving long acting [Inaudible]. Thank you.

Man: Are you an endorsing provider?

Jim Gasparich: I am not.

Man: You are not. And do you know that if you are an endorsing provider and write DAW you can get whatever you want without having an interruption of care.

Jim Gasparich: I do know that.

Man: Is there a reason why you're not an endorsing provider?

Jim Gasparich: Probably just a matter of not having filled out the paperwork.

Man: I might comment...

Jim Gasparich: And I actually think...I don't know what percentages of people are endorsing providers. You guys probably know, but I don't.

Man: Well, it depends on how you cut it, but it's probably 50 plus percent of the major prescribers for Medicaid and UMP. I might comment that in this class this is one of the highest classes of the DAW rates, you know, somewhere close to 25% DAW in this class. So there are a lot of providers that are taking the option of DAW as an endorser.

Jim Gasparich: And I can readily see that because I mean, truly, I mean...and I'm not trying to pull the wool over anybody's eyes here. I mean from a clinical perspective I think these drugs are so much better than the generic form. I think it's hands down and I could understand why people would do that because you have to if you want the patients to take it. I really think the state will save more money because I think Medicaid pays for incontinence pads and so it's kind of like offering to pay for that. Maybe they should pay a little bit more for the drug and get one that the patients will take.

Man: Well, thanks a lot.

Man: Yeah, thank you. Um, next is Dr. Dave Gross. Dave?

Dave Gross: Thanks for having me back again. I didn't change my suit, but I have changed my hat. So we're not talking about Aricept now. We're going to be talking about Detrol LA. As I stated earlier this morning I am a clinical pharmacist with Pfizer Pharmaceuticals and a lot of what I was going to say was covered previously so I won't belabor that at all. I just wanted to go into a little bit more detail about DeBeers List or DeBeers criteria that was mentioned by a couple of speakers earlier. DeBeers list identifies potentially inappropriate medications routinely used in the elderly. Now I know this was not included in the Oregon EPC report because the only thing included there are evidence based while this document is not evidence based in its entirety it does represent the consensus opinion of subject matter experts in the area. It's also routinely referenced as the standard of care for medication use in the elderly and is also used by the Centers for Medicare and Medicaid Services or CMS when they are going to decide which charts to review when they go and do an audit of a nursing home facility.

In the most recent update that was published in December 2003 in the archives of Internal Medicine, "Immediate release Oxybutynin as stated was included as an example of medication to be avoided in the elderly due to its anti-cholinergic properties." Now I commend the reviewers, but if you look at the different studies...the amount of anti-cholinergic side effects were all over the place. If you refer back to the package inserts for the products and you look at Oxybutynin and Oxybutynin extended release the incidents of dry mouth as an example of an anti-cholinergic side effect is somewhere in the 60 to 61% out of the package insert. If you look at the package insert for Detrol LA that same side effect, dry mouth, which is the number one anti-cholinergic side effect for this drug class is listed at 23%. To me that is a statistically significant difference. In the absence...the absence of a long-acting agent for the treatment of OAB on the Washington Preferred Drug List coupled with the designation, the current designation of immediate release Oxybutynin as the preferred drug in its class this could be viewed, I think, as a direction to the providers of the elderly to basically disregard the very document, that being DeBeers list that is routinely endorsed and cited as a standard of care for medication use in the elderly. So I would appreciate it if you could take this information into your decision-making and offer an extended release form of overactive bladder product on the preferred drug list and I would encourage you

to make that Detrol LA since it does have a decrease incidents in anti-cholinergic side effects based in studies and in the package inserts for the products. Thank you for your time and I appreciate it.

Man: Thanks. I'm working off of a number of different lists here, but Dr. Bruce Smith.

Bruce Smith: Good afternoon. I mirror a lot of the comments that we've heard from the panel and the speakers already. Oh, I'm sorry, I'm Dr. Bruce Smith. I'm a full-time practicing Geriatrician and so your comments about cognitive effects are particularly germane in my practice. I spent the last 18 years in geriatrics discontinuing this class of drugs by enlarge and staying away from it for the most part. I would agree with other speakers that the long-acting preparations are somewhat better tolerated and I am an endorsing provider and I take advantage of that at times. But I speak today in encouraging you to add the newer agents of Solifenacin and Darifenacin in particular to an expedited review, if possible, so that at least if they are reviewed even though you may not choose to make it a preferred drug, if I had the option of writing for those medications for the next six months it would be especially helpful. Reviewing these drugs next December will be a moot point for seniors because they all go off Medicaid drug lists in January when Medicare [Inaudible] hits the road here. Particularly Darifenacin that I've had some experience with the last few months is a different class of drugs as far as seniors and the cognitive side effects. They have a couple of papers that show that the risk or the rate of cognitive effect is equivalent to placebo even at high dose. That is not at all the case with any of the existing drugs. The long-acting preparations of the existing drugs are better tolerated but people still get very cognitively impaired particularly if they have other co-existing illnesses or taking other medications. So my plea is I would agree with the other speakers that the short acting Oxybutynin causes major problems in my nursing home practice because other friends of yours from the state come by and slap our hands when we use that, but Darifenacin in particular seems to be much better tolerated if we could get an early review so that I would have the option of signing for that, it would be very helpful rather than waiting six months.

Man: Thank you.

Man: I might comment that we do authorize those scripts. They are under prior authorization. We do give 30 days and then have you come back and tell us whether it is needed. Nicole informs me that quite often we don't see a repeat for another 30 days because I think in this class [Inaudible] profile regardless of whether it's, you know, the generic or the brand are quite significant and that's what we're seeing at least in our authorization.

Woman: Yeah, since January when the first one was available, the newer ones we were given...started giving them a 30-day, you know, and asked for feedback after that. We have never had anybody since then come back asking for another 30 days. So that's one of the conclusions is that it's not any more effective and the side effects...they experienced the same as the others and didn't continue it.

Man: [Inaudible]

Woman: Yeah.

Man: Was there any other stakeholder input? Did I miss anybody? I think I have gotten everybody. Okay, so in terms of...just reminding the committee of our last review of this class of medications was in March of 2004 and on page 15, again, under the tab of drug review history is our recommendation and it looks like it is abbreviated here, Erika, but I'm assuming that...thank you. I would rather be safe than right. That's what I thought. So Tolterodine and Oxybutynin are found to be safe and efficacious in treatment of irritable bladder without regard to special population. That is how our recommendation read last time. I'm wondering if, at this point, if anybody on the committee wants to speak to that form of recommendation.

T. Vyn Reese, M.D.: This is Dr. Reese. Actually, Tolterodine is misspelled it looks like in the old one. The question is, these drugs were all...these all have a lot of side effects and the question is Tolterodine does have less, you know, dry mouth associated with it. It may have less CNS toxicity or it may not. It's unclear there. All drugs that you should use with an extreme caution in the elderly. If these new drugs coming on the market actually are significantly different that will be interesting, but we don't have that data and we're not...we can't act on that today. I think that generic Tolterodine and generic Oxybutynin should both be available to providers. I don't think we should choose between those two. I don't think the long-acting preparations are, from what we looked at, that significantly different. These drugs all have huge discontinuation rates. As I'm looking through here after six months 68% have quit Tolterodine and 78% have quit Oxybutynin. So people don't stay on them for long periods of time. The long-acting drugs don't look...they look like they are a little bit better, but not much. So the drugs aren't...the side effect profile for these drugs is not good. I think Tolterodine may be a little more tolerable in dry mouth, but the short acting has the same advantage of as the long acting. So I think we may...I think there is an argument that we could probably put it on as the generic Tolterodine on in addition to Oxybutynin.

Man: I don't think there is a generic form of that.

T. Vyn Reese, M.D.: On the short acting?

Man: It says...is there a short acting form of the Tolterodine?

Man: So it's not generic yet.

Man: [Inaudible]

T. Vyn Reese, M.D.: Okay, then I'm mistaken. That sort of makes it a moot point. In any case these drugs are not...they are not great...they have to be used with great care in the elderly and all of them are bad according to what I've learned about them. They can be used in other patients that are younger and are not cognitively impaired. I'm afraid of them all, actually.

Angelo Ballasiotes: I think the next time around or whatever we really need to focus on the cognitive issues on the medication. I think that should be a question that directly...

Man: [Inaudible] is that not correct? The cognitive issues?

Man: I will have to check on it, but I believe they have been or else we are finishing those...our next meeting, which is within...yeah, the first of July. So I'll make sure they get added to that.

Angelo Ballasiotes: Thanks.

Man: Other...Jason, I'm wondering if you have any comments.

Jason Iltz, Pharm. D.: Not at this time.

Man: I'll just put a comment out for further discussion just in terms of sort of how we have been thinking about our recommendations. Let's see what others think. Earlier when we were considering the Alzheimer's meds we looked at relatively soft data on GI side effects. Now I know that the context was a little bit different, but still it came into play. We, unfortunately, as people have mentioned don't have...we don't have good data on cognitive side effects with respect...comparatively. I mean we know all of these drugs can cause cognitive side effects and I'm just...I'm wondering whether people feel any need to be consistent in that regard in this case or if people see it differently.

Woman: I agree here. In looking back this was a year plus ago that we did this and our format was quite different. So I think maybe we need to look at this and number one Tolterodine is not generic. So if that is something we said last year we should maybe put, you know, Detrol LA instead. I don't know how we change this. And also with regard to special populations I agree that we should add something here because it doesn't seem to me that this is the same thing in the elderly. I think we need to change this. We also need to change irritable bladder to whatever we are calling it.

Donna Marshall, Pharm. D.: Dr. Carter, this is Donna Marshall. Typically, we haven't mentioned the brand names. If we mention a generic formulation of a drug if it's only available as a brand then it's the brand that would be preferred.

Woman: Then we would want to say Tolterodine long-acting or just Tolterodine.

Donna Marshall, Pharm. D.: However you want to state it, but we've been not usually specifying brand names in the recommendations. We've been sticking to the generic name of the drug.

Woman: I'm not going to make a motion yet, but I think in this case we really need to make a new recommendation.

Man: The question is what? That we don't...you don't want to put any of them on the formulation? I mean that's...

Man: There is no [Inaudible].

Man: Yeah, right. Take them off the Preferred Drug List all together. I mean until we look at a newer agent. That's another option. So it's like...the question is...

Jeff Thompson, M.D.: This is Jeff Thompson, again, you know, under the Preferred Drug List the endorsing providers are exercising their options to write DAW for non-preferred. This is the highest non-preferred rate that we have in any of the classes. I'm just giving you the straight facts. When you do list the drugs in just their...not generic name, but chemical name then you are asking staff to basically compare prices and hopefully the drug manufacturers will give us good prices and if they do then there is generalized access to all drugs. When they differentiate themselves on price, but not differentiate themselves on any clinical efficacy, safety or special population then we generally are seeing not usually one, but typically two or three drugs that come up and are preferred.

Patti Varley, ARNP: This is Patti Varley. Do I recall correctly that we can say within this, using generic names, we can also specify that a long-acting agent be available. If we chose to we can choose to include that in our statement. Is that not correct?

Man: Yes, the whole point of using the chemical name is that if it later becomes generic we don't have a problem with saying that wasn't your decision in retrospect. So we try...that's the only...

Man: And the example where you differentiate that is the anti-diabetic medications you did differentiate the short acting and long acting and stated that there was no difference in the short acting and long acting and therefore on the Preferred Drug List we only have the short acting. And then again on that drug class we did see an increase in the DAW rate likely related to the preference of the endorsing providers for the long acting. So if you do indicate that, that will take that up under consideration in the bid and look at both short and long acting.

Carol Cordy, M.D.: Can I take a shot at this and then we can destroy it?

Man: Sure.

Carol Cordy, M.D.: Okay, so after considering the evidence on safety and efficacy and I'm leaving out special populations for the first round here.

Man: Just to make clear this is Dr. Cordy making the motion.

Carol Cordy, M.D.: Sorry. On safety and efficacy for the treatment of overactive bladder I move that Oxybutynin and Tolterodine are effective.

Man: Excuse me. Do you want to include the new drug, Trospium also?

Carol Cordy, M.D.: It's not in the study.

Man: It's in this review. Trospium is in this review.

Carol Cordy, M.D.: Oh, Trospium. Oh, not the other two. And Trospium, yeah. And then I think just from what we're saying, and we can delete all this, that Oxybutynin is associated with...or let's do it the other way around. Tolterodine...and I'm not sure if the stage of that is clear on Trospium are associated with fewer adverse events in the elderly.

Man: We don't have that data.

Man: You're talking about dry mouth.

Carol Cordy, M.D.: Well, fewer adverse events in everybody then.

Man: I think...and it may be...you may be correct.

Carol Cordy, M.D.: Okay. This is just to shot...we're doing this differently.

Man: Carol, if I could recommend...I would just comment in terms of what we have on the summary slide is...with respect to side effects really is in long acting versus short acting preparations and shows less dry mouth with the longer acting preparations and that's really what we have that is consistent in terms of, you know, I would say in terms of the data. I'm just thinking in terms of working, maybe picking up where you are starting...I'm thinking that we could potentially say that these medicines are, you know, safe and effective and that we recommend that there be a long acting preparation available and that we make maybe some additional comment on the use of these medicines in the elderly.

Man: The thing is that the long acting preparation may not be actually better if you're looking at exactly the same preparation as far as dry mouth goes. It looks like that Tolterodine is better than Oxybutynin in dry mouth and then in the...there is a suggestion that long acting Tolterodine may be a little bit better than immediate release in my reading.

Man: Well it...I'm not...my overall reading is that there is little difference that we have been presented here. It shows little difference between the extended release or long acting preparations. You know, on withdrawals and on dry mouth that really...and really the comparison is with short acting versus long acting and so if you're going to comment on long acting it would be in that respect and that would be the case for saying you should have a long acting preparation.

Man: Dan.

Daniel Lessler, M.D.: Yeah?

Man: If you are looking to better educate and communicate to the provider community certainly we can take this up in the DUR activity and do a special project where we go out and communicate to those providers around the issues of "the short and the long acting, the generic and the brand," which might be more effective at getting the message out than, you know, trying to craft something that will just go up on the web site.

Daniel Lessler, M.D.: What I'm concerned about is that I think that if we say that we think that long acting Tolterodine is better, it's still associated with...can be associated with serious side effects in the elderly so both cognitive side effects and others. So I don't think we can say it is safe to use. I think we should just say, after these agents, we say "Caution should be used in using these agents in the elderly." Something like that, some sort of caution needs to be included with both of them, with any of them that we know so far. Now the newer agents may be safer, we don't know, but the ones that we have available they should be used with caution.

Patti Varley, ARNP: This is Patti Varley. I'm just going to look back here at least at the summary of evidence statement. To me that at least directly addresses one of these questions having to do...it says comparative efficacy between the two head-to-head trials do not provide sufficient evidence of clinical significant differences between either agent and either the immediate release, the extended release or the TD formulation. That's the summary. So...

Man: That's with respect to efficacy. So then the other side of the equation is safety and what I'm saying is...what I think the take home message here is that the data we have are moot to these very important cognitive issues. The only data that we have comparatively to really decide whether or not we want to, you know, and how much we want to influence we want to influence our decision is around...that I see here is really around dry mouth and that I think a general statement is in extended release there is less dry mouth than in...regardless of the specific preparation than in short acting. I don't know if whether that is...

Duane Thurman: This is Duane Thurman. I guess that's fine to make a statement in that, but remember that the point of the motion is to give the agency something to take away that after the result of our cost analysis will make sure that the drugs that you want available are on there. The fact that these may not be appropriate or there may be safety concerns, but then I don't think we will solve that by your recommendation necessarily, but that falls back onto the practitioner. The question that we need is to make sure that what your decision is today allows us to put the drugs on the list as you see it. So if there is adding a long-term preparation or a...

Man: Right. Well, the question is, are there compelling reasons to specify that a long term preparation should be available. That's what we're talking about.

Duane Thurman: I just don't know that you need to explain the reason in the motion.

Man: I know, I know, but to get there we need to have a reason.

Woman: Looking again at the summary though it does say short-term studies indicate that...maybe [Inaudible] formulations cause more dry mouth and overall adverse events. So if we're going to say...I don't think we should stop at dry mouth.

Man: Right. After considering that...

Janet Kelly, Pharm. D.: This is Janet Kelly. In the exact same thing there it says, "But withdrawal rates were not significantly higher." So the incidents of side effects was higher, but didn't make any difference on how people continued therapy or not.

Man: This is [Inaudible] with DOC. The decision is going to effect as well, but here is my question exactly. When you are talking about the side effects are they clinically significant or are they statistically significant? The numbers shows, yes, they are showing it to be higher, but the number of the withdrawal, if it's not as much then it makes it to be not significantly different in clinical outcomes.

Man: Right.

Man: Points well taken.

Nicole: This is Nicole with Medicaid. I have one concern...that's a question I have. If you believe like Dr. Reese if eventually DeBeers and any of these others possibly like Detrol could be added to DeBeers when they are updated. It took awhile. They just recently added off the [Inaudible] 2003. I wonder if once they have more data and usage of...what's, you know, your thoughts and something to consider.

Man: Nicole, let me give you...

Man: We're talking about drugs that we haven't reviewed yet. We're not talking about these two drugs, we're talking about drugs that we have not reviewed in front of the committee and there was a question about whether we should expedite reviews as some of these other drugs, which we can't do. We basically are limited to the drugs that we have here today and we have to decide how we are going to manage these drugs since we haven't reviewed the others.

Nicole: I was talking about...you said that you were afraid of any of these drugs like Detrol, you know, if you think...it's not on DeBeers now, do you think it could be added to DeBeers in the future or...

Man: It may be. It certainly...if you look at the list of side effects it's the same. And it's an anti-cholinergic drug and it probably does get into the brain, too. So it may not be as bad as Oxybutynin, but it certainly is a major caution and it's highlighted in all the reviews of these drugs. So I wouldn't feel safe just because you have somebody on that. The other newer classes of drugs may be safer, but I don't have that data to look at today so all we have is what we can look at today. And if there is really not...if there is no generic preparation for Tolterodine now that we can add, then we are sort of stuck adding...looking at just these two drugs, one of which is a generic short acting and one is only in a long acting preparation or in a short acting that is not a generic.

Man: Actually, Donna, or Erika, I'm sorry. You guys switched seats. Um, could you just go back to the last year's recommendation? I believe what's different is we have Trosipium as well, but again to remind people, a year ago the motion that passed was Tolterodine and Oxybutynin are found to be safe and efficacious in treatment of irritable bladder without regard to special populations. Actually, I'm wondering if we haven't sort of come back to that as we've had this discussion, but has been helpful in terms of flushing out the various issues and some of the subtleties here, but given what has been said around clinical significance versus statistical

significance and clinical significance perhaps being and I think this is probably where we were at last year around withdrawal rates and given that we have no data on cognition and would like it and will get it in the next review, I would argue that we're pretty much where we were a year ago.

Woman: I don't think we are quite where we were. I think we have some concerns about the safety, not just in the elderly, but in everybody—somebody who is driving or whatever. And I think we want to reflect that we have that concern. And I think, at least from the summary here, there is somewhat of a difference between the side effect profile and the adverse events and the long acting and the short acting and that's in the report. I think we should reflect those two.

Man: What I think we need to do is, you know, I think the long acting and the short acting; the discontinuation rates are basically no different. Okay? So it really...the real problem is I think we need to add caution in use in the elderly. It's a special population that's at risk for these drugs. Okay? And I think that other drugs down the line we may find are safer to use for this indication, but I think we need to make sure that in our recommendation that's a special population where we need to give a warning.

Man: I guess just to get clarity as a staff member if you are doing that are you telling us to prior authorize a certain age group? I mean when you do those safety concerns usually I interpret that as a direction to do something as it relates to utilization controls. Again, if you are concerned about just education and communication we would be more than happy to do this as a DUR function as we have done in a number of drug classes.

Man: Let me...if it's a cognitively intact person the question is should you be cautioned about using it? You know? And they might be able to tolerate fine, but you have to make sure that the provider knows that this may cause a problem if somebody is cognitively impaired.

Man: So my sense is that there...our momentum is to want to go into an area of cognition where we have no data, but we have a lot of concerns. So with that in mind actually and given that these...there is going to be new data and a re-review when Jeff...

Jeff Thompson, M.D.: It's going to be coming out in December, which we could probably put on the December meeting.

Man: So in six months we could...and that would include cognition as well and we could then address those issues. What I'm going to suggest is that we actually table this until then, which would mean that the current recommendation...that effectively would keep the current recommendation as is and that we not try and craft a new motion at this point because we really...we don't have the information that it is sounding like we all want to have.

Man: Okay.

Man: And it will come out either immediately...because then it will be a new drug formulary with a different...[Inaudible]. So...

Man: Well...

Man: You need a motion at the table.

Man: Is there a motion at the table?

Man: So moved.

Man: So moved.

Man: Okay. Second?

Man: Second.

Man: Okay. All of those in favor say Aye.

Group: Aye, Aye, Aye

Man: Opposed? Same sign. Okay, thanks.

Man: Can we get who made the motion and the second?

Jason Iltz, Pharm. D.: I made the motion.

Man: And Angelo seconded it.

Man: We are transcribing the meetings now and so it is very important for people to...

Man: Right. So we are going to move on then to the last agent, which also is an update, which is oral hypoglycemics and Jeff, did we have OHSU for this?

Jeff Thompson, M.D.: No. If you saw the report there is hardly anything in the update.

Man: So just looking at the update again I think there really is not much new here since our last set of recommendations. I do believe that there are some stakeholders who wanted to comment on oral hypoglycemics and Dr. Weiss are you still...Andrew Weiss? Again, if you could identify if you are here with a sponsorship or a manufacturer, thank you.

Andy Weiss: I'm Dr. Andy Weiss. I'm a clinical pharmacist with Novartis Pharmaceutical. I'm here today to talk a little bit about Starlix. I think we all know the epidemiology part about diabetes so I'm not going to go over that. Suffice to say that the majority of those patients, 75% of those with type 2 diabetes will die from coronary vascular disease. On average, sufferers will die 5 to 10 years earlier than those not affected by the condition. Starlix or Nateglinide is a novel derivative of the amino acid diphenylalanine. It's indicated as mono therapy to lower blood glucose in patients with type 2 diabetes, also known as NIDDM. This hyperglycemic cannot be

adequately controlled by diet and physical exercise and who have not been chronically treated with other oral anti-diabetic products.

It's taken in an oral tablet form up to 30 minutes before main meals three times a day. It addresses the problem of post meal time glucose spikes similar to the one I'm getting right now primarily from that large lunch I had.

Epidemiological research has shown these glucose spikes to be an important independent risk factor for cardio vascular and mortality in patients with type 2 diabetes, which are known to contribute to elevated glycosylated hemoglobin. Starlix acts directly on the pancreatic beta cells to stimulate early short-acting insulin secretion in patients with type 2 diabetes. This type of diabetes the extra glucose in the blood cannot be metabolized quickly enough resulting in postprandial glucose spikes. This early phase insulin response is the body's first defense against these post mealtime glucose spikes. It's indicated as initial mono therapy and in combination with Metformin or Thiazolidine in patients whose hyperglycemia is inadequately controlled with Metformin or after therapeutic response to a TZD. Starlix may be added to but not substituted for these drugs.

Using Starlix to improve post-meal glucose control results in enhanced overall glycemic control is reflected by reduced hemoglobin A1C levels, which is the gold standard for measuring long-term control. These efficacy benefits are achieved with low rates of mild hyperglycemia and low level weight gain, but without other treatment emergent differences relevant to placebo. It's been on the market since 2001. Are there any questions about the agent? Thank you.

Man: Dr. Matt Kresken(?).

Matt Kresken: Well, thank you. My name is Matt Kresken. I am a PharmD with Sanofi-Aventis Medical Liaison here in Seattle. I would like to take a moment and thank the group for having me here and allowing me to speak and I wanted to elaborate on Andy's nice discussion on cardio vascular disease and diabetes especially as it relates to Glymepiride, the brand name which is Amaryl. There has been a number of studies throughout the years on a topic called ischemic preconditioning and I wanted to bring this up to the group to kind of bring this to the forefront regarding Glymepiride and we can have a discussion about this afterwards. But I wanted to talk about the data on Glymepiride and ischemic preconditioning. As you probably know ischemic preconditioning is the heart's natural protective mechanism and how this occurs is the potassium channels in the heart open up following up a myocardial insult in ischemia. Following that potassium channel opening thus prevents further damage during subsequent ischemia. Now when you block those potassium channels with a sulfonurea, which closes potassium channels and there are differences in the sulfonureas and where they close those potassium channels. Amaryl is more specific for the pancreas than it is to the heart and when you look at the data with Amaryl versus Glyburide, Glymepiride versus Glyburide in ischemic preconditioning what you see is there is a difference in ST segment changes, as well as subjective cardiac chest pain. What this shows is a significant reduction as to segment changes for Glymepiride versus Glyburide and when you look at the incidence of heart disease in the diabetic population I know it's 2 to 4 times the incidence...

Unknown: [Inaudible] ...secondary prevention and we've seen that in all the data etcetera with the recommendations as well as all the AmErikan Diabetes Association Recommendations. I think this is a very important thing to think about in all of our diabetic population that every [Inaudible] in terms of outcome is for cardiovascular disease. And when you think about what one wants to do, I would urge you to consider Amaryl or Glymepiride as one of the agents for hypoglycemics. Having said that, that's one part of it, the other part is we've all heard the discussion about physician preference of long-acting drugs and that just may come up after we're done with our testimony. It's a once daily drug. The other topic is hypoglycemia. This drug has shown significantly less hypoglycemia than Glyburide. No head-to-head studies with Glipizide. But when you look at Glyburide it's significantly less in the MacGregor paper that was looked at in the Oregon Review. Another paper that has come out recently looked at...a prospective observation looked at Glymepiride vs. Glyburide and what they saw was roughly a six fold decrease in severe hypoglycemia for Glymepiride as compared to Glyburide. And we can talk about the [Inaudible] cost of hypoglycemia, but when you look at this once daily formulation, the cardiac differences in this drug, which [Inaudible] maybe and looking at this as a biased opinion. But when one looks at this clinically, there are people, internationally renown endocrinologists around the company [Inaudible] Portland, Oregon who has written an editorial on this topic and said, Maybe it's time to retire Glyburide based upon these cardiovascular differences in these two drugs. The other thing that...in the area here in Seattle here recently was at Madigan Army Hospital recently changed Glyburide to Glymepiride based upon this data. And just a little inside information...don't sell your stock yet. But this drug is actually going generic in November. I know this kind of perks everyone's ears up, right, that the drug is going generic in November, so one thing you could potentially consider put [Inaudible] on the [Inaudible]. I don't mean to [Inaudible] but it's something to consider. I think the data is there. I think this is a better drug than Glyburide for [Inaudible] cell. When you look at these cardiovascular benefits, hypoglycemia benefits, the once a day compared to just the short-acting Glyburide [Inaudible]. So something to consider. And I'll take any questions at this point. Thanks.

Daniel Lessler, M.D.: Thank you. Thanks a lot. And that's all the folks I think I had down for oral hypoglycemics. Did I miss anybody? Okay. Erika, can you [Inaudible]...still do it here? Okay. So this is the motion or the recommendation of the committee from last March, I'll read that: Chlorpropamide, Tolazamide, Tolbutamide, Glymepiride, Glipizide, Glyburide, [Inaudible] micronized, Nateglinide and Repaglinide are efficacious in the treatment of Type II diabetes. A [Inaudible] metabolized drug with inactive metabolize needs to be on the Preferred Drug List for those patients with renal insufficiency. And that's where we were in March of 2004 when we first considered these agents. And I'll ask if anybody looking at the update and so forth has anything to add or sees reason, at this point, to make changes to that.

So, Jason, are you there?

Jason: I still am, yeah.

Daniel Lessler, M.D.: Okay.

Man: Way to hang in there, Jason.

Daniel Lessler, M.D.: So, do you have the language we've been using...maybe I can put that in a...if I could ask someone to actually put that forth as a formal motion after Donny gets that up there.

Man: So do you want me to enter the old motion as the new language?

Daniel Lessler, M.D.: No, [Inaudible]...what we've been doing on all the others. After reviewing...right.

Patty Varley: This is Patty Varley and I'll make the motion that after reviewing the updated information on updated oral hypoglycemics, our previous March 17th, 2004, recommendation remains in effect.

Daniel Lessler, M.D.: Is there a second?

Man: Second that.

Daniel Lessler, M.D.: Okay. Then any further discussion? All right. All those in favor say aye.

Many: Aye.

Daniel Lessler, M.D.: Opposed [Inaudible]. Okay, motion carried. And actually this is...this then concludes the P and T portion of our meeting. And I think what we'll do is reconvene at maybe 3:00. That gives us about seven minutes or so. And, Jeff, I'm wondering if you can talk fast.

Jeff: We'll speed it up.

Daniel Lessler, M.D.: So we'll reconvene at 3 for the DUR portion. Thanks.

DUR Board Meeting Minutes
June 16, 2005

**WASHINGTON STATE PHARMACY AND THERAPEUTICS COMMITTEE
MEETING**

Regular Meeting

Radisson Hotel SeaTac

2:00pm – 4:00pm

Council Members Attending: Daniel Lessler, MD, Patti Varley, ARNP, Carol Cordy, MD, Robert Bray, MD, T. Vyn Reese, MD, Angelo Ballasiotes, Pharm D., Jason Iltz, Pharm D., and Janet Kelly, Pharm D.

Medical Assistance Administration, Coordinating Staff: Jeff Thompson, MD, MAA Chief Medical Officer; Nicole Nguyen, Pharm D, Clinical Staff Pharmacist, MAA;

L&I staff

I. ADMINISTRATIVE ITEMS

The meeting was brought to order by chairperson Daniel Lesser, MD. The minutes of the previous DUR Board Meeting in March, 2005 were approved.

II. Mental Health Drug Initiative

Dr. Thompson, MD summarized the progress of the Mental Health Initiative workgroup's evidence-based mental health drug reviews. The slide presentation is attached. Nicole Nguyen, PharmD presented the workgroup's prior authorization agreements on the off label use of the second line anticonvulsants (gabapentin, Keppra, Topamax, and Gabitril), and the duplication of second generation antidepressants. Dr Nguyen also presented the results of the duplicate second generation antidepressant prescriber survey in March 2005. There will be expedited prior authorization codes to allow these four anticonvulsants to be filled without any stops when used for the FDA approved indications. Time will be allowed to taper patients off of these medications. Larry Martin, MD presented the evidence for the off-label use of the second line anticonvulsants and the proposed criteria for use.

III. Antiepileptic Drugs for Neuropathic Pain Guidelines

Jaymie Mai, PharmD presented the draft guidelines for the use of the second line anticonvulsants for neuropathic pain. L & I and MAA met May 18, 2005 with actively prescribing pain specialists to review the evidence and develop treatment guidelines. DUR Board members were asked to review the guidelines and send comments to either Jaymie Mai or Lavonda McCandless.

III. MANUFACTURERS' PRESENTATION

None

IV. STAKEHOLDERS' PRESENTATIONS

None

V. RECOMMENDATIONS OF COUNCIL

The DUR board was in support of the initiatives and commended the workgroups on the work they did. It was suggested to provide good communication and education to the prescribers and make use of the workgroup members to help with this in their communities. The concern was also expressed of how the pharmacist will receive the diagnosis from the prescriber with the least burden to the providers. It was discussed whether the pharmacy was required to have all the patient's diagnosis's on file and whether the prescribers should write the diagnosis or diagnosis code on the prescription.

ADJOURNMENT